



PHD

## Chemical modification of polysulfone

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## Abstract

The research presented herein is concerned with the chemical modification of polysulfone towards the synthesis of a hollow fibre boronic acid fixed carrier membrane system for saccharide separation.

Chapter 1 firstly introduces the area of boronic acids as chemosensors, in particular for detecting saccharides. Secondly, membrane separation techniques are discussed focussing on hollow fibre membranes and their synthesis.

Chapter 2 discusses the potential of boronic acid fixed carrier hollow fibre membranes for saccharide separation. Three general routes are highlighted to achieve the desired boronic acid appended polymers: electrophilic aromatic substitution, lithiation and functional monomer polymerisation.

Chapter 3 describes the various attempts at achieving the target polymer *via* electrophilic aromatic substitution methodology.

Chapter 4 describes the various attempts at achieving the target polymer *via* lithiation methodology.

Chapter 5 investigates the ability to create functional monomers with which functional polymers can be polymerised from.

Chapter 6 describes the synthesis and characterisation of the compounds discussed in chapters 3, 4 and 5.

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## Abbreviations

|                 |   |
|-----------------|---|
| Å               | Ångström  |
| Ar              | Aryl  |
| AIBN            | 2,2'-Azobis(2-methylpropionitrile)  |
| <sup>t</sup> Bu | Tertiary butyl  |
| °C              | Degrees Celsius   |
| CMPO            | <i>n</i> -Octyl(phenyl)- <i>N,N</i> -diisobutylcarbamoylmethylphosphine oxide |
| δ               | Chemical shift in parts per million downfield from trimethylsilane            |
| DCM             | Dichloromethane   |
| DCME            | Dichloromethyl methyl ether   |
| DMF             | Dimethylformamide   |
| DMSO            | Dimethylsulfoxide   |
| DS              | Degree of substitution  |
| HERG            | Human hepatocellular carcinoma  |
| HMQC            | Heteronuclear multiple-quantum correlation                                    |
| Hz              | Hertz   |
| ICT             | Internal charge transfer  |
| IR              | Infrared  |
| <i>J</i>        | Coupling constant (in NMR spectroscopy)                                       |
| m               | Multiplet   |
| MPBH            | Methylpentanediolborane   |
| <i>m/z</i>      | Mass-to-charge ratio (in mass spectrometry)                                   |
| NIPS            | Non-solvent induced phase separation  |
| NMP             | <i>N</i> -Methylpyrrolidone   |
| NBS             | <i>N</i> -Bromosuccinimide  |
| NMR             | Nuclear magnetic resonance  |
| nm              | Nanometres  |
| μm              | Micrometres   |
| MOMCl           | Chloromethyl methylether  |
| NPOE            | 2-Nitrophenyloxyether   |
| Ph              | Phenyl  |
| PET             | Photoinduced electron transfer  |
| PES             | Polyethersulfone  |
| PSF             | Polysulfone   |
| Psi             | Pounds per square inch  |
| Ppm             | Parts per million   |
| Pr              | Propyl  |
| PVP             | Polyvinylpyrrolidone  |
| q               | Quartet   |
| R <sub>f</sub>  | Retention factor (chromatography)   |
| rt              | Room temperature  |
| s               | Singlet   |
| sLex            | Sialyl Lewis X  |
| SLM             | Supported liquid membrane   |
| t               | Triplet   |
| TBA             | Tetra- <i>n</i> -butylammonium  |
| TCE             | Tetrachloroethane   |
| THF             | Tetrahydrofuran   |

|       |                                    |
|-------|------------------------------------|
| TICT  | Twisted internal charge transfer   |
| TIPS  | Thermally induced phase separation |
| TMSCl | Trimethylsilyl chloride            |
| $t_R$ | Retention time                     |
| TMEDA | Retramethylethylenediamine         |
| UV    | Ultra violet                       |

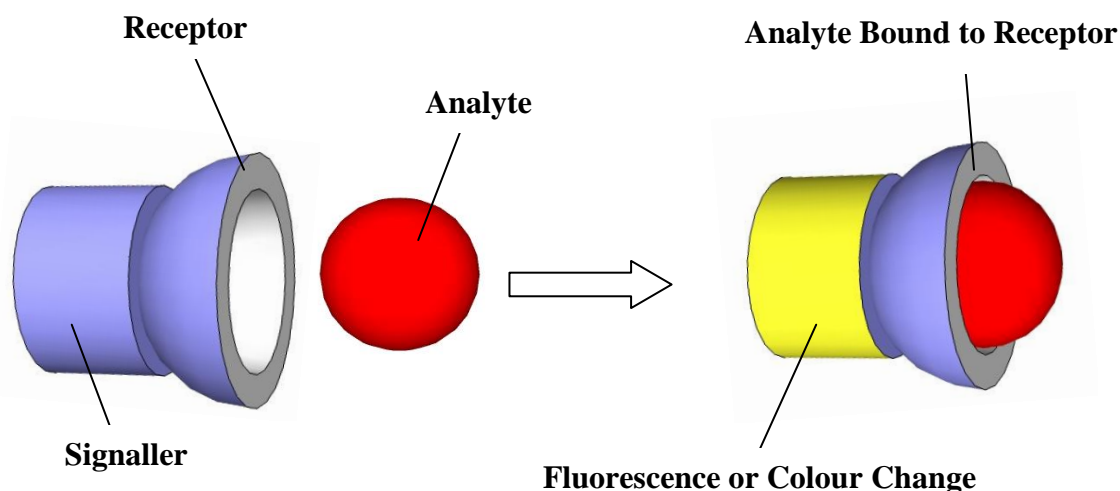
## Chapter 1 : Introduction to Boronic Acids and Membranes

### 1.1 General Introduction

Identification of chemical and biological substances is a very important task and the need to quickly and accurately determine a substance is at the heart of chemical, medical and environmental issues, be it the determination of a compound in a chemical synthesis, a test for an antibody in a patient or impurity levels in drinking water. The identification and separation of saccharides from various mixtures is of great importance, be it glucose levels in diabetes sensors, detection of oligosaccharide disease biomarkers or the purification of natural sugar mixtures for industrial purposes such as bio fuel manufacture or food additives. Chemosensors (chemical sensors) can be made to specifically detect, interact and report the presence of target analytes (such as sugars) even when the target is in a complex solution. Various membranes, especially Hollow Fibre membranes, can be used to separate or concentrate substances from mixtures, including saccharides.

### 1.2 Chemosensors<sup>1,2</sup>

Chemical sensors generally involve two parts; a receptor and signaller (**Figure 1.1**). Similarly to receptors present throughout biological systems, the receptor should interact perfectly with a target analyte. This can be in the form of bonding interactions (hydrogen bonds, reversible covalent bonds, ionic bonds) or electronic interactions (dipole interactions) and this interaction instils a change of geometric or electronic configuration on the receptor. The change on the receptor is then referred to the signaller and the signaller conveys to the outside world what the receptor is interacting with. With chemosensors this is usually done by either a fluorescent or a colourmetric signal as shown in **Figure 1.1**. By adjusting the receptor and the signaller, the sensor can be modified to react to a specific chemical in a specific manner.



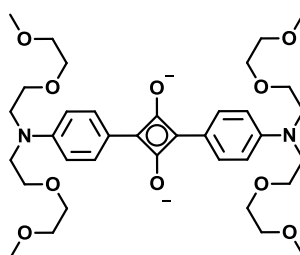
**Figure 1.1:** Diagram of sensor/analyte interaction and signalling.

Chemical sensors exist specifically to detect a large range of different chemical functionalities including: amines, alcohols, aldehydes, amino acids, carbon dioxide, cyanides, fluorides, hydrogen sulphite, hydrogen disulfide, thiols, and most importantly, saccharides and oligosaccharides. The binding and the signalling work in a variety of ways and under a variety of conditions (aqueous, organic, pH, temperature etc.).

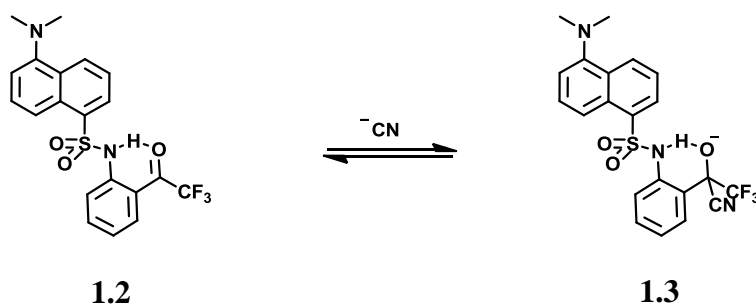
There are a number of noteworthy examples of chemosensors which clearly demonstrate the principle.

### 1.2.1 Cyanide Detection

Ros-Lis *et al.*<sup>3</sup> synthesised a colourmetric sensor based on a squaraine ring **1.1**. When dissolved in acetonitrile it gives a strong blue colour at  $\lambda_{\text{max}} = 641 \text{ nm}$  due to the strong charge transfer bands between the outer chains and the delocalised central ring. Addition of cyanide ions leads to nucleophilic attack on the central ring and disruption of the delocalisation, which in turn stops the charge transfer from occurring. This leads to the colour changing from blue to colourless on contact with cyanide ions.

**1.1**

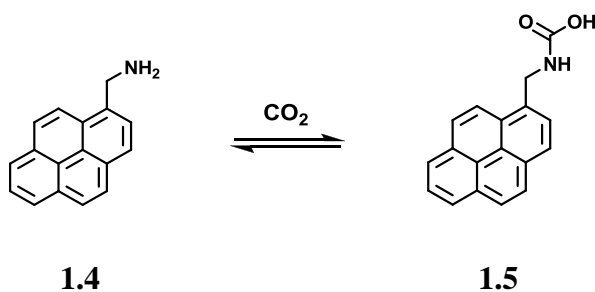
Chung *et al.*<sup>4</sup> developed a fluorescent cyanide sensor based on a naphthalene sulphonic acid amide moiety **1.2** (Scheme 1.1). When attacked by cyanide ions (**1.3**) the sensor shows a fivefold increase in fluorescence intensity emitted at  $\lambda_{\text{max}} = 500\text{-}530$  nm. The hydrogen bond formed between the amide and the neighbouring carbonyl group stops potential quenching routes by both inferring conformational rigidity to the sensor and by blocking deprotonation of the amine, the importance of this being shown by the inactivity of the *para*-derivative.

**Scheme 1.1**

### 1.2.2 Carbon Dioxide Detection

Hamep *et al.*<sup>5</sup> devised an elegant and simple method for the quantitative detection of carbon dioxide. Aminomethylpyrene **1.4** reacts with carbon dioxide to form the carbamic acid **1.5** in polar aprotic solvent (Scheme 1.2). This reduces the quenching effect of

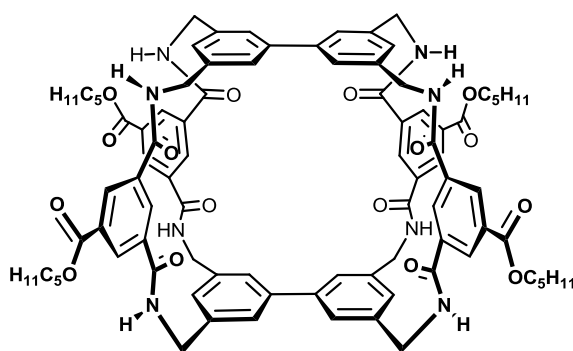
nitrogen's lone pair on the pyrenes fluorescence, thus the fluorescence is enhanced at 408 nm when excited at 341 nm.



**Scheme 1.2**

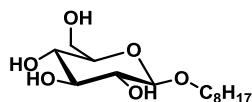
### 1.2.3 Saccharide Recognition

Davis *et al.*<sup>6</sup> based their design for saccharide sensor **1.6** on the *Escherichia Coli* galactose binding protein. Their biomimetic approach followed nature closely, with a large pocket surrounded by hydrophobic groups to encourage encapsulation of the sugar. The sugar interacts with the receptor *via* numerous carbonyl and amide groups, forming hydrogen bonds.



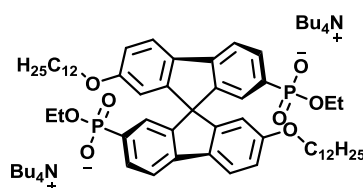
**1.6**

The sensor **1.6** shows good binding to octyl- $\beta$ -D-glucoside **1.7** in chloroform, but this gets weaker with the introduction of aqueous solvent.



**1.7**

Das *et al.*<sup>7</sup> designed sensor **1.8** around phosphonate hydrogen bonding. The relatively rigid nature of the chiral spirobifluorene central core allowed a fixed binding site for sugars to be achieved, leading to increased binding.



**1.8**

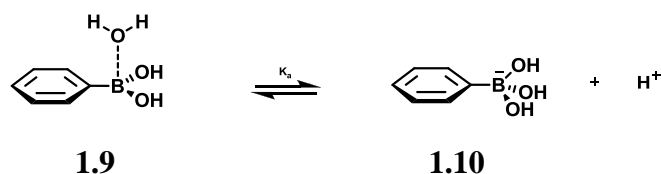
The problem with these saccharide sensors in comparison with the aforementioned sensors is that the receptor-analyte interaction is based on hydrogen bonding and dipolar interactions which are relatively weak when compared to, for example, the covalent interactions of the cyanide sensors. This leads to major problems with the analyte being displaced from the receptor by the solvent system, hence why the mentioned sensors only tend to work in organic solvents. Biological systems have the ability to completely remove water from their binding pockets, but this is impractical in a synthetic system so other means must be used.

### 1.3 Boronic Acid Chemosensors<sup>8-10</sup>

Boronic acids covalently interact with 1,2 and 1,3 diols and thus are well placed for the manufacture of saccharide sensors as they would not face the problems associated with aqueous media. As such, boronic acids have received the largest amount of attention and have yielded the best results in terms of saccharide recognition.

Initial studies showed interactions between boric acid and saccharides allowed the configurational determination of glucose *via* monitoring changes in acidity and conductivity following their complexation.<sup>11</sup> The interaction between the boron diol system and saccharides was further investigated with phenylboronic acid and various sugars which led to the structure and mechanism of the boron sugar interaction being clarified.

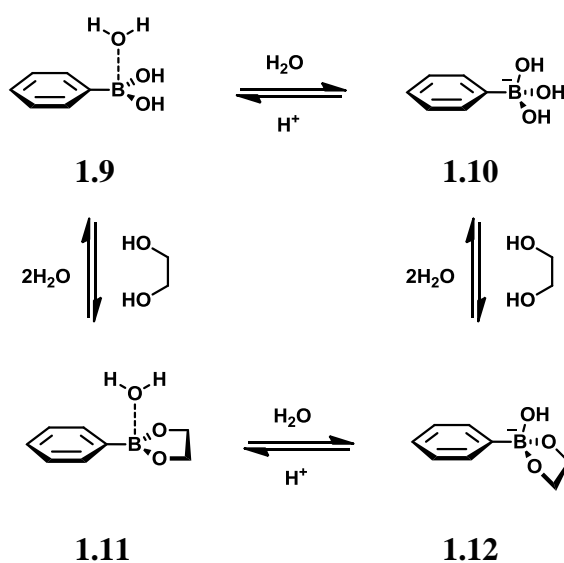
Phenylboronic acid **1.9** has the boron in a  $sp^2$  hybridised state. It was found that in aqueous media the boron was in fact in equilibrium with its  $sp^3$  hybridised state, with water interacting with the boron's empty p-orbital to form **1.10**. In fact, the water is in rapid exchange on the boron, showing a  $pK_a$  of 8.70.<sup>12</sup>



**Scheme 1.3**

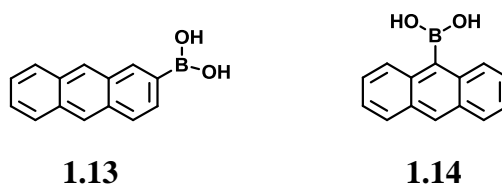
The addition of saccharides to phenylboronic acid follows the same route as water, but the diol of a saccharide displaces two equivalents of water to create a cyclic boronate ester, 5 or 6 membered depending on whether complexing with a 1,2 or 1,3 diol (**Scheme 1.4**). The conversions are very dependent on pH due to the large amount of proton shifts involved.



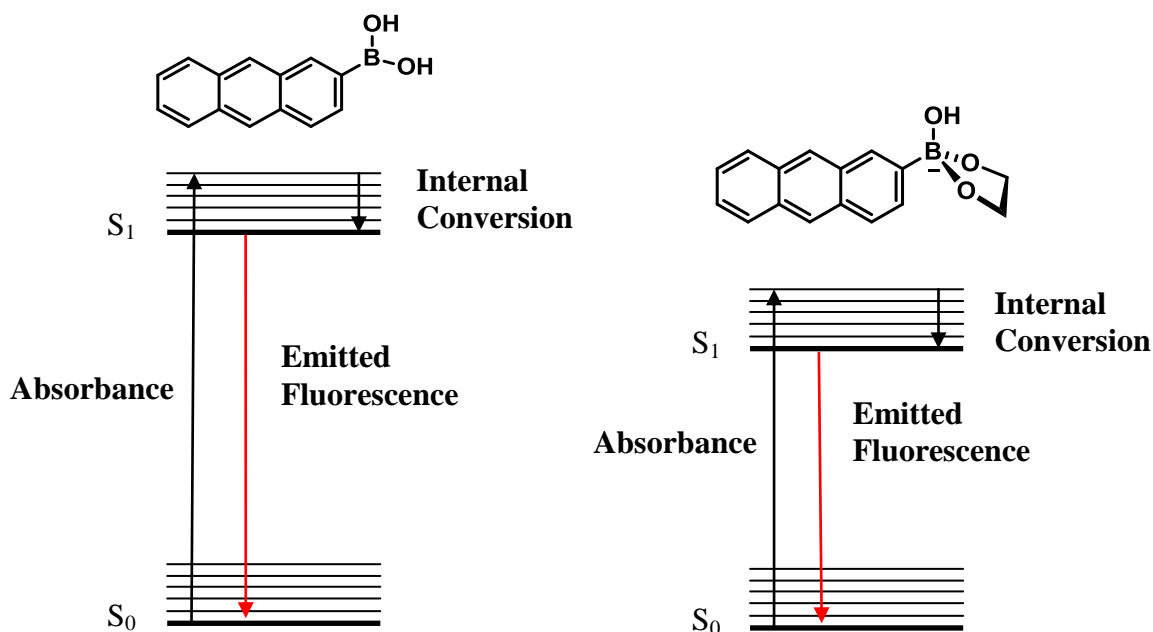


Scheme 1.4

The first attempt to take advantage of the boronic acids' saccharide binding ability was by Yoon *et al.*<sup>13</sup> with the coupling of a boronic acid to a fluorescent anthracene unit **1.13** and **1.14**.



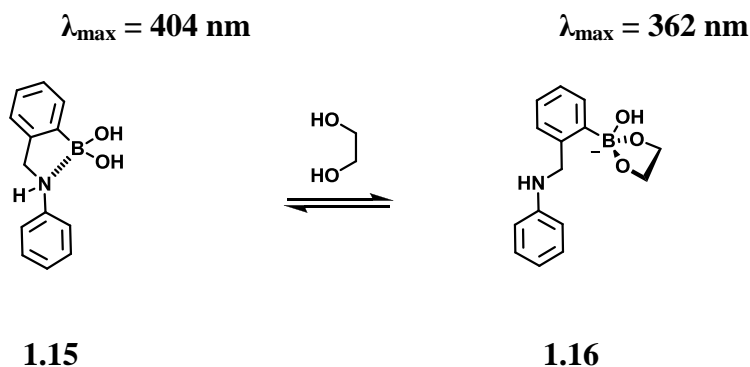
Upon complexation of the saccharide in a pH 7.4 solution, the boronate ester formed quenches the anthracenes fluorescence (**Figure 1.2**). This reduction in fluorescence intensity under complexation of saccharides allows the molecule to act as a sensor. Both isomers show a greater selectivity for fructose than other sugars.



**Figure 1.2:** Jablonski diagram representing quenching of the fluorescence of anthracene boronic acid upon diol binding.

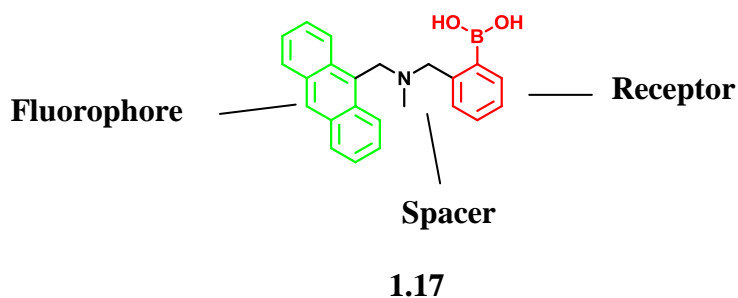
An improvement on this system was achieved by Sandanayake *et al.*<sup>14</sup> and expanded by Bosch *et al.*<sup>15,16</sup> Taking advantage of boron's empty p-orbital, they produced a sensor which rather than showing a decrease in fluorescence intensity upon saccharide binding, gave an emission at a different wavelength instead.

The amino-methyl group of **1.15**, *ortho* to the boronic acid, donates into the empty p-orbital, creating an interaction (**Scheme 1.5**) with the nature of this interaction subject to debate. In the resting state, the position of the nitrogen's lone pair orthogonal to the  $\pi$ -system of the benzene ring allows so called "twisted" internal charge transfer to occur, giving a fluorescence of 404 nm. Upon complexation with saccharides to form **1.16**, the nitrogen-boron interaction is broken, leaving the nitrogen's lone pair free to conjugate with the  $\pi$ -system, stopping the TICT and giving an increased emission blue shifted to 362nm.



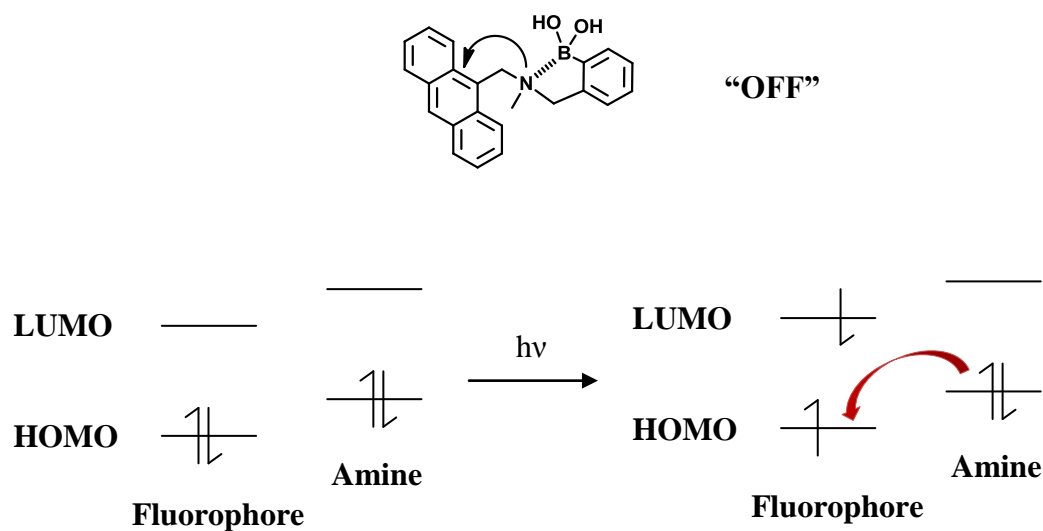
Scheme 1.5

A further development of this was achieved by James *et al.*<sup>17,18</sup> with the exploitation of a fluorophore-spacer-receptor design, as depicted in **Figure 1.3**. A spacer basically consists of any group that separates the receptor group from the fluorophore, breaking any conjugation between the two and preventing the typical inductive type effects seen with simpler sensors. The easiest way to achieve this is by inserting a methyl group between the fluorophore and the amine linker.

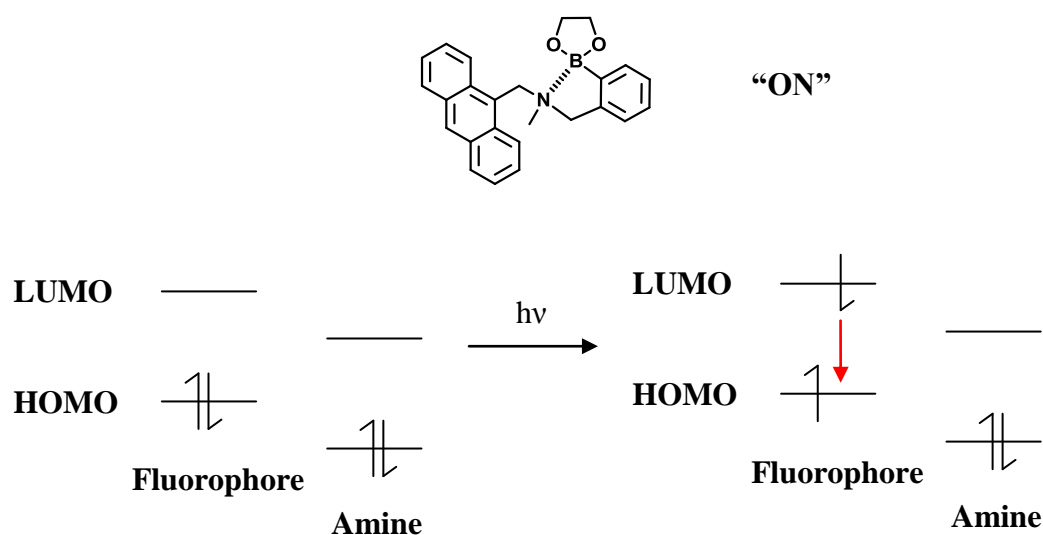
**Figure 1.3:** Fluorescent saccharide sensor with fluorophore-spacer-receptor motif.

When the fluorophore is excited, an electron transfer occurs across the spacer from the receptor (specifically the lone pair of the nitrogen) which is then followed by a non-radiating internal conversion, effectively strongly quenching the fluorescence. This type of fluorescence quenching is known as photoinduced electron transfer (PET). Upon complexation of a saccharide, the PET process is greatly reduced, resulting in a large

increase in fluorescence intensity. This is demonstrated in the molecular orbital diagrams **Figure 1.4** and **Figure 1.5**.

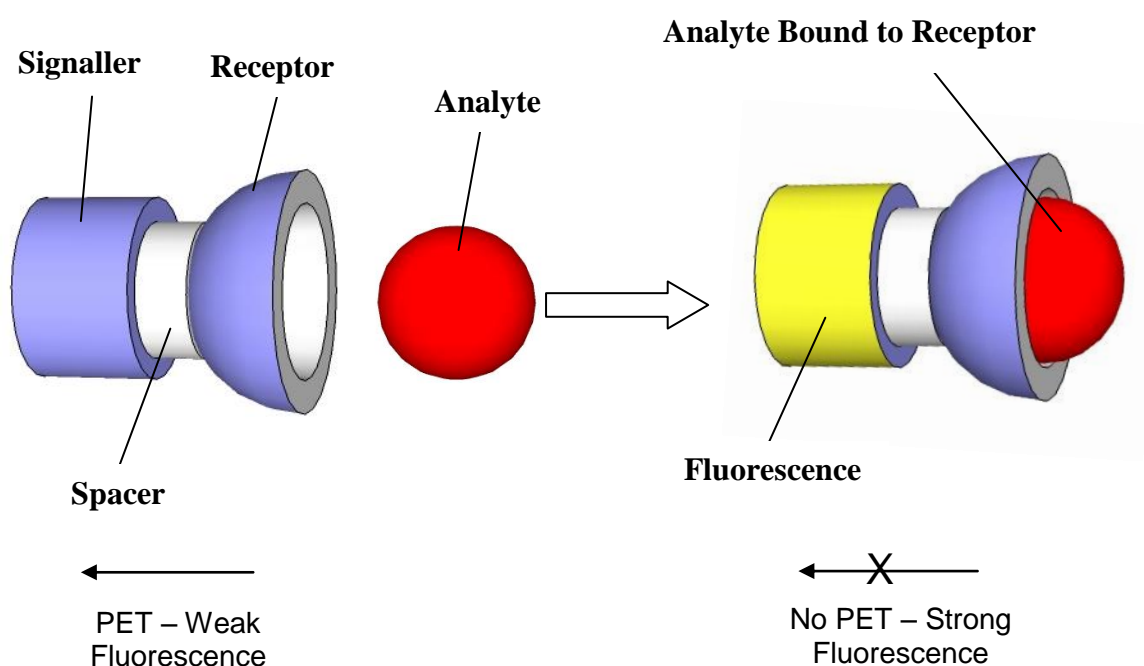


**Figure 1.4:** Molecular orbital diagram representing the PET quenching of the unbound fluorescent sensor.



**Figure 1.5:** Molecular orbital diagram representing the fluorescence achieved upon diol binding.

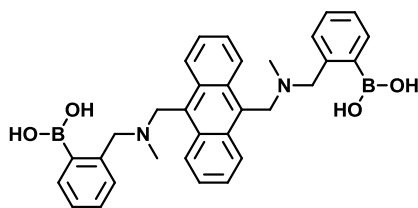
The PET process almost entirely quenches the fluorescence of the unbound sensor, leaving it in a so called “off” position. Upon binding with a suitable diol, the Lewis acidity of the boron centre increases, due to the greater level of  $sp^3$  hybridisation of boronate esters versus boronic acids. This leads to a stronger boron-nitrogen interaction and as a result a much weaker PET as the nitrogen’s lone pair is too tightly bound to the boron. The removal of the PET effect allows the fluorophore to fluoresce, effectively switching it “on” (Figure 1.6).



**Figure 1.6:** Diagram of PET “off-on” fluorescent sensor.

The aforementioned boronic acid sugar sensors, whilst proving the concept, are still very limited in design. They all show greatest selectivity for fructose. Whilst this is useful for making a fructose sensor, the ability to make the sensors specific for desired sugars is needed.

A modification of the anthracene PET sensor **1.17** with the addition of a second boronic acid unit lead to the sensor **1.18** being selective for glucose rather than fructose.<sup>19</sup>

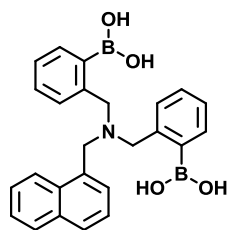
**1.18**

This is important for two reasons. Firstly, glucose sensing has major applications in medical sensing for diabetes; sensing of the glucose levels in patients is currently achieved *via* glucose oxidase enzymes, which has a number of flaws. Secondly, it shows that it is possible to tailor boronic acid sensors to specific sugars.

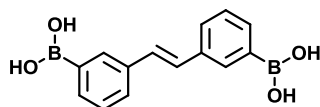
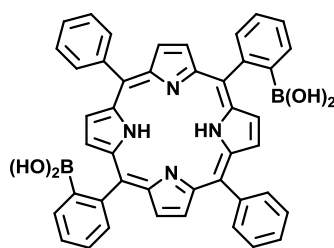
Monoboronic acid's selectivity for fructose is due to it being able to form a complex with the sugar with the optimum bond angles and distances of the formed boronate, as discussed in section **2.2.1**. A diboronic acid sensor on the other hand isn't about the individual interaction, as the two boronic acids combine to effectively create an overall binding site. The pocket of the above diboronic acid sensor **1.18** is perfect for D-glucose and the cyclic boronate ester formed is more stable for D-glucose than other sugars. The fluorescent response is dependent on binding at both sites as only this will stop the PET and allow fluorescence.

So, if the binding on diboronic acid sensors is based on the geometry of the molecule, then altering the positions and lengths of the chains (the linkers) should alter the specificity of the sensor.

Reduction in linker size for example, has been shown to favour smaller sugars, for example **1.19** favours D-sorbitol over other sugars. This is due to the boronic acids being so close together that larger sugars such as glucose could not fit in the binding pocket.<sup>20</sup>

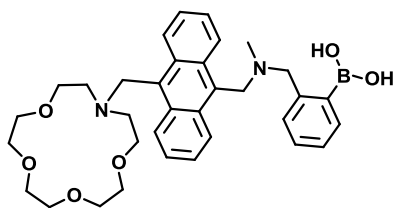
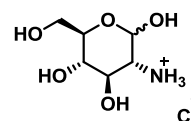
**1.19**

Two other good examples are the systems **1.20** and **1.21**, selective for two more complicated sugars, the disaccharides melibiose<sup>21</sup> and lactulose<sup>22</sup> respectively. Again both provide the perfect binding pocket for the respective sugars.

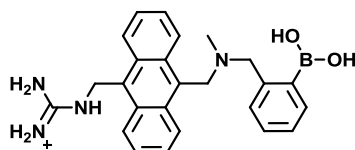
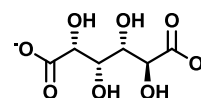
**1.20****1.21**

The eventual aim of the saccharide detection is to be able to detect more complex oligosaccharides. Whilst this may prove difficult to achieve by just altering the linker, the complexity of the molecules can be exploited.

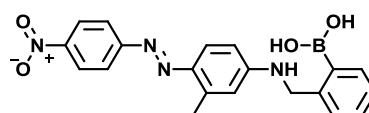
For instance, Cooper *et al.*<sup>23</sup> developed a monoboronic acid sensor **1.22** selective for ammonium appended sugars, such as D-glucosamine hydrochloride **1.23**. The azocrown ether, replacing the second boronic acid, complexes with the ammonium group and not the diols, thus the sensor is specific for ammonium appended sugars over regular saccharides.

**1.22****1.23**

Similarly, Wang *et al.*<sup>24</sup> developed a sensor **1.24** to interact with sugars containing carboxylate moieties. In this case, a guanidinium group complexes with the carboxylate section of D-glucarate **1.25**, while the diols bind to the boronic acid.

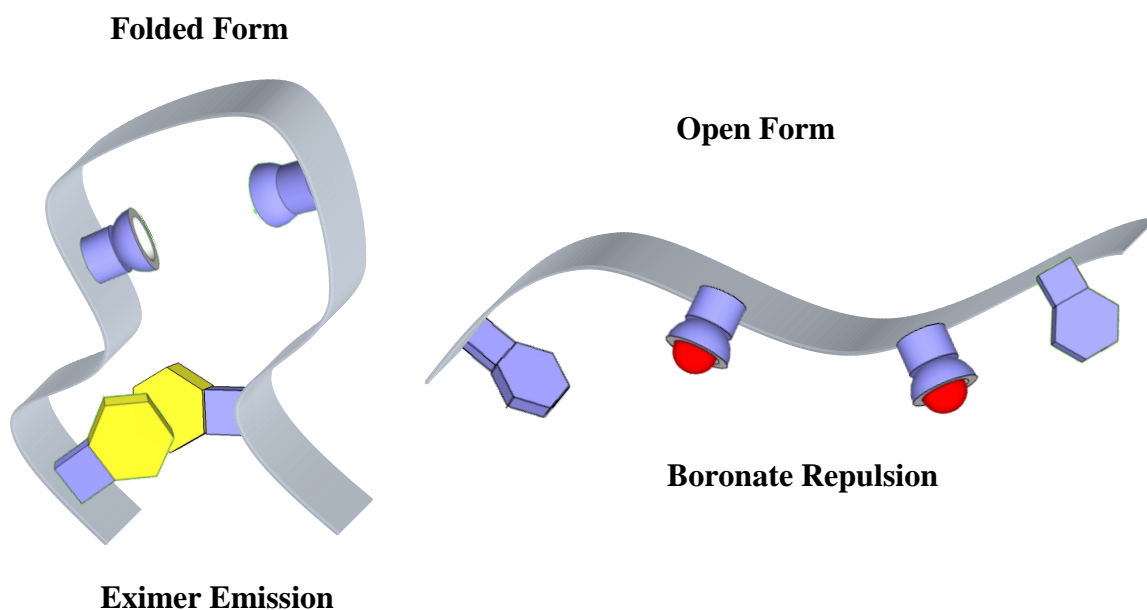
**1.24****1.25**

Boronic acid sugar sensors are not limited to fluorescent sensors. A range of colourmetric sensors, based mainly on azodyes and metal complexes have also been reported. For example, James *et al.*<sup>25</sup> have prepared a range of sensors, including **1.26**, which changes from purple to red upon saccharide complexation.

**1.26**

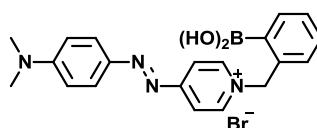


A completely alternative type of fluorescent sensor is the incorporation of boronic acids within polymer hydrogels (**Figure 1.7**). Complexation of saccharides with the boronic acids in the polymer either pulls together or repels the polymer strands, causing fluorophores to stack or unstack, resulting in a gain or loss of excimer emission.



**Figure 1.7:** Boronic acid hydrogel fluorescent saccharide sensor.

Boronic acids also function equally well as fluoride and cyanide ion sensors.<sup>26</sup> Badugu *et al.* synthesised boronic acid hemicyanine dyes, such as **1.27**, with fluorescence on complexation of cyanide ions, even under physiological conditions.

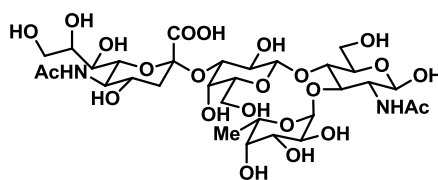


**1.27**

### 1.4 Boronic Acid Oligosaccharide Sensors

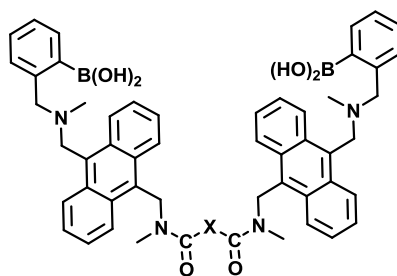
Whilst there has been a lot of research into sensors for small to medium saccharides, sensors for oligosaccharides have not been so forthcoming, likely because of the harder task of making a sensor for such a complicated molecule.

Initial work has been done by Yang *et al.*<sup>27</sup> on the synthesis of a sensor for the cell surface oligosaccharide sialyl Lewis X (sLex) tetrasaccharide **1.28**. This oligosaccharide is a suspected biomarker for certain cancers such as hepatocellular carcinoma, which has problems with late stage diagnosis.



**1.28**

A standard design of a diboronic acid sensor (**1.29**) was examined with an extensive range of linker units (represented by X) to investigate whether the needed geometry could be achieved to be selective for sLex.



**1.29**

Of all the linkers investigated, the fluorescence of the sensor in solution with sLex increased the most when X was a phenyl ring. This indicated that the phenyl linker gave the optimum sensor geometry.

The sensor was then tested with HEPG2 cells with sLex markers bound to the cell surface, as well as with HEPG3 cells with Lewis Y (Ley) markers, another related biomarker. The sensor was able to label the HEPG2 cells and didn't label the HEPG3, showing that it had very high selectivity. Another sensor, with the linker X as *ortho*-xylene, labeled the HEPG3 cells, but not the HEPG2 cells, again, showing the selectivity that can be achieved by altering the linker.

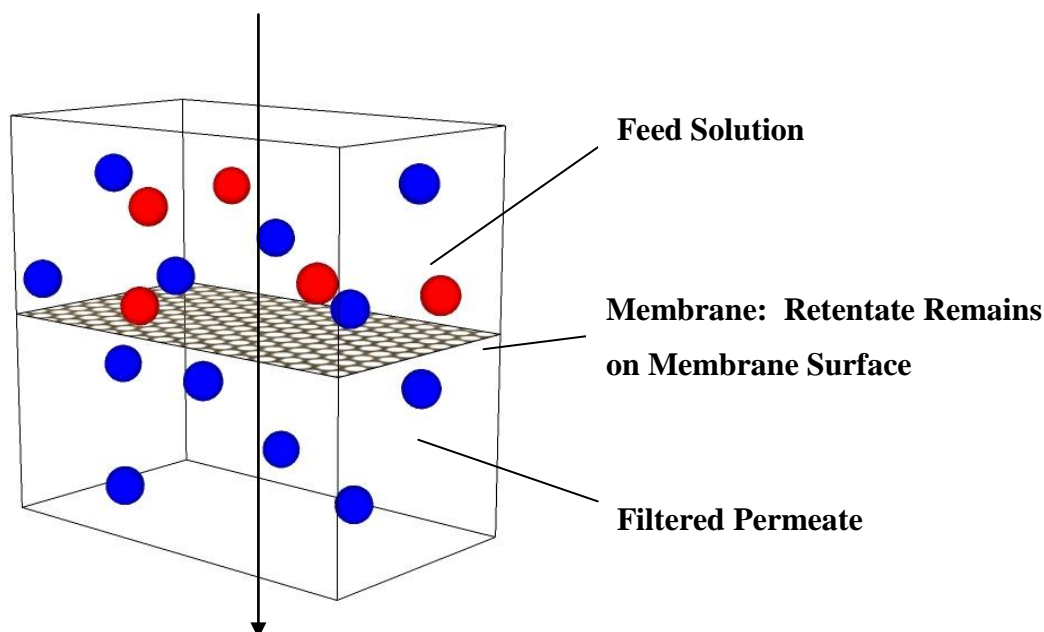
With this as an example, it is highly likely that a system such as this could be successfully used to tailor a diboronic acid fluorescent sensor to the as yet unknown oligosaccharide biomarker and thus label and detect the cancer cells or the shed fragments of the cell surface.

## 1.5 Membranes<sup>28-30</sup>

Membranes are barriers through which desired materials can permeate whilst others cannot in order to separate a mixture of materials. Most commonly membranes are used to separate molecules from a solution, for example, molecules entering cells through cell wall membranes. However, they can also be used in liquid-liquid, liquid-gas and gas-gas separations. The driving forces for the separations are usually passive transport effects: pressure, temperature or concentration gradients; the movement from high to low pressure, temperature or concentration. There are also active transport effects such as the movement of ions *via* an electrical potential. Membranes can be classified by the size of the permeate they pass and by the method with which they separate it.

### 1.5.1 Traditional Membranes

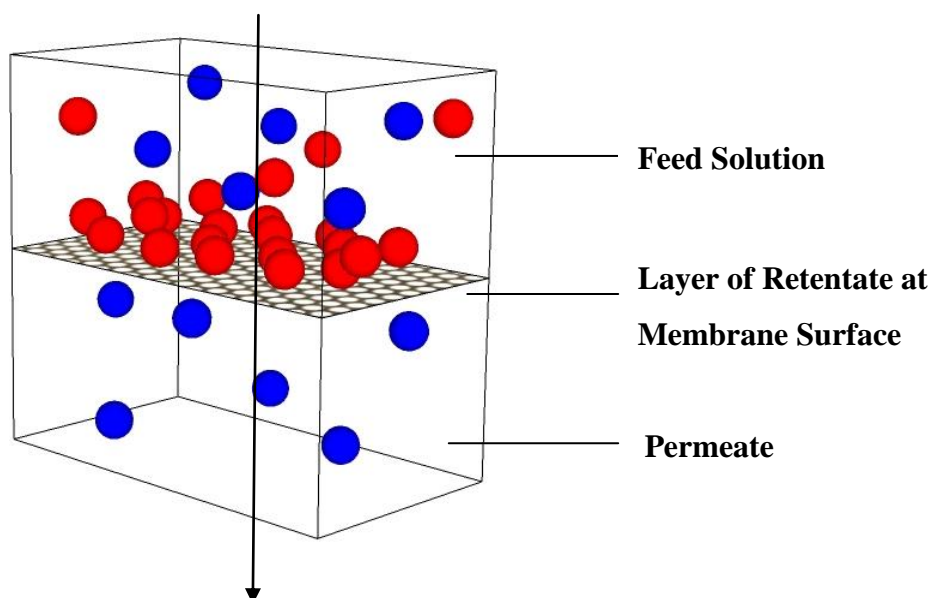
Traditional membranes consist of flat, “dead-end” membranes (**Figure 1.8**), for example filtration using filter paper membranes. The feed solution is passed against the membrane, with the permeate passing through and the retentate remaining at the membrane. They commonly are used with gravity controlling the transport.



**Figure 1.8:** “Dead-end” membrane.

There are a number of advantages of traditional membranes. They allow continuous separation such that filtering continues as new feed is added and does not need stopping and restarting as is the case with chromatography columns for example. They also have low energy consumption; they are generally not “powered” and in the cases that they are, consumption is small. The process can be directly scaled up from laboratory to industrial scale and can be operated at variable temperatures. Since they do not require high temperatures they are suitable for heat sensitive applications such as with food, drugs and enzymes.

However, traditional membranes also have some disadvantages. A potential problem is concentration polarisation which is demonstrated in **Figure 1.9**. As the permeate passes through the membrane, a thin film of non-permeating or slow permeating material builds up on the feed side of the membrane as the permeate continues to pass through. Eventually, the amount of non-permeating or slow permeating material at the interface means that the effective concentration of permeating material is lower on the feed side than on the permeate side of the membrane, and this reduces the flux.



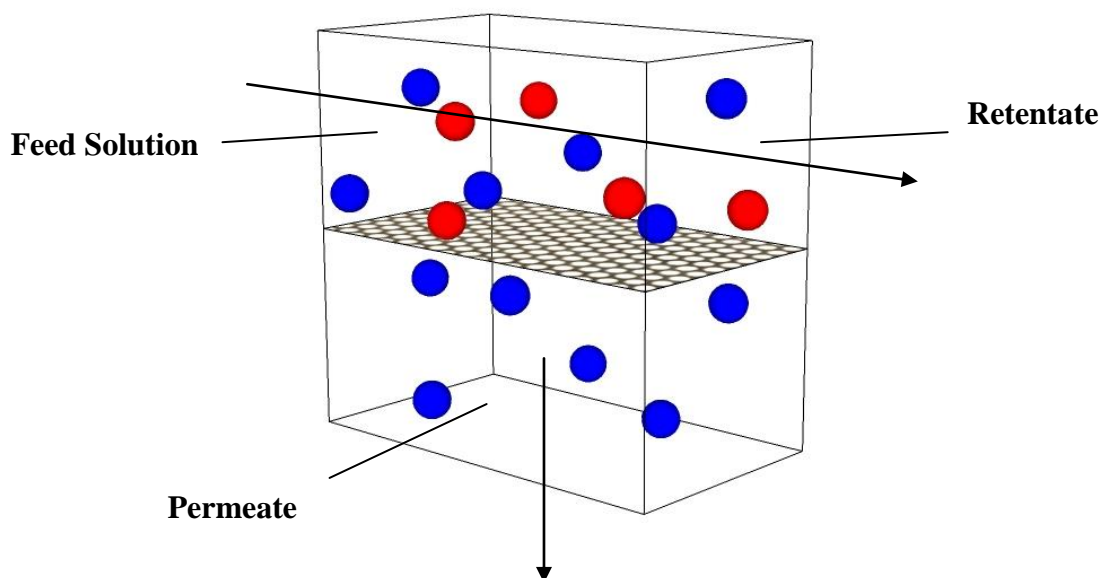
**Figure 1.9:** Concentration polarisation effect on “dead-end” membrane.

Fouling is similar to concentration polarisation. Instead of it being a concentration effect, the non-permeating material forms a cake that physically blocks the pores of the membrane. This reduces the amount of material that can permeate and thus reduces the flux.

A further disadvantage can be low selectivity. The membranes are mainly size exclusion selective and thus can only separate things of varying sizes, unlike other techniques which may use polarity, charge or boiling point.

Compared with other techniques, the flux of traditional membranes is much lower and their lifetime shorter. This is due to the nature of the materials the membranes are made out of.

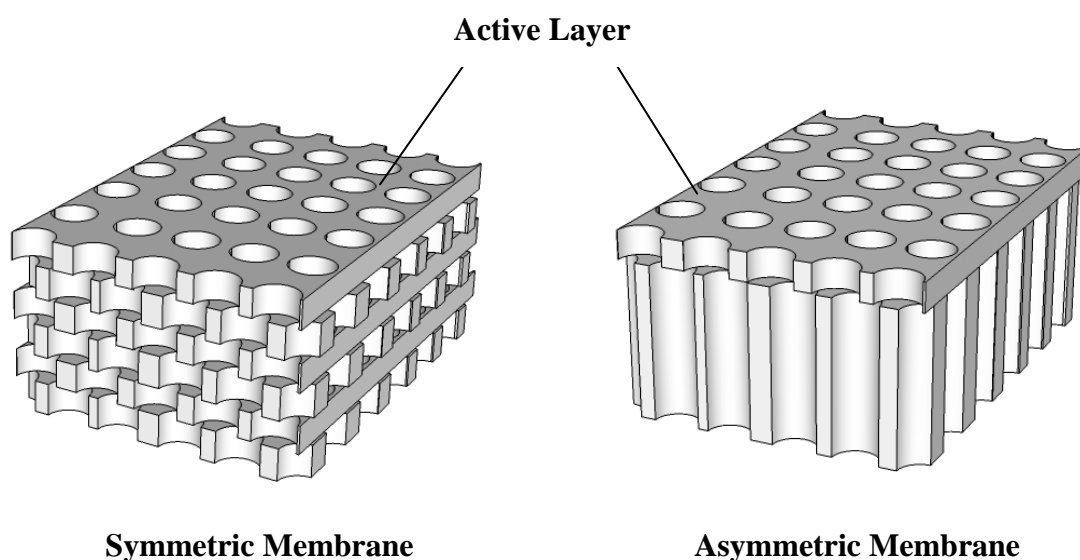
A major advancement over the traditional “dead-end” membranes was the development of the “cross-flow” membrane. Instead of the feed being forced against a membrane and the retentate remaining at the membrane causing problems of concentration polarisation and fouling, the feed travels parallel to the membrane, allowing the permeate to be removed perpendicularly to the flow and thus, causing the retentate to be removed away from the membrane (**Figure 1.10**).



**Figure 1.10:** “Cross-flow” membrane.

With the feed constantly moving across the membrane, any retentate that would normally settle and foul or cause concentration polarisation is removed. This keeps the flux of the membrane much higher than “dead-end” membranes. Fouling and concentration polarisation still occur, but at a much reduced level.

Another major advancement was the advent of asymmetric membranes as shown in **Figure 1.11**. Symmetric membranes have pores evenly throughout the membrane layer. The rate of permeation, the rate at which the permeate travels through the membrane, is inversely proportional to the thickness of the active layer of the membrane; the thicker the bit of the membrane responsible for the size exclusion, the slower the filtration. So, a membrane will have the best performance with the thinnest active layer. The easiest way to achieve this effect, rather than making very thin membranes, is to make an asymmetric membrane where the active layer sits on top of a larger, supporting layer.

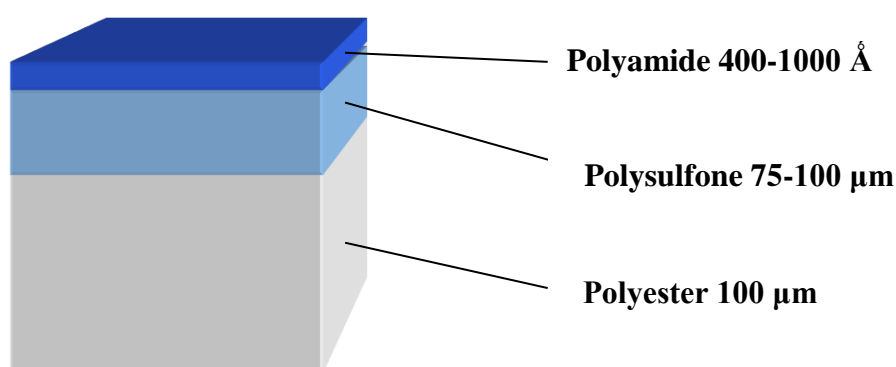


**Figure 1.11:** Cross-section of symmetric and asymmetric membranes.

**Figure 1.11** also shows that the symmetric membrane has a continuous porous structure. The active layer encompasses the entirety of the membrane, thus its efficiency is reduced from having to pass the permeate through more of the active layer than is necessary.

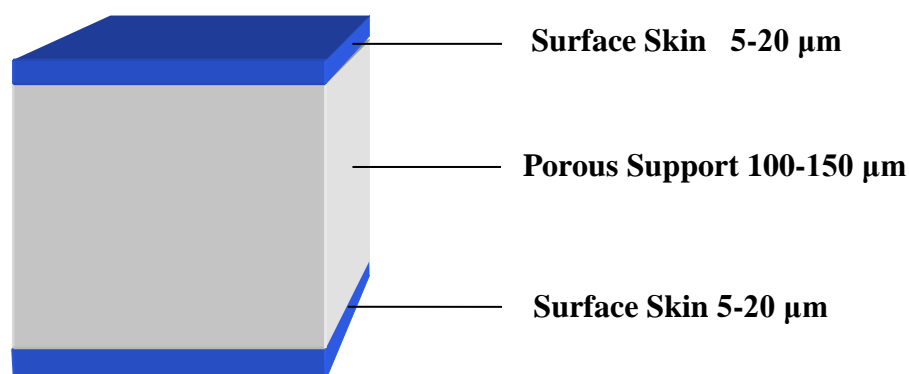
The asymmetric membrane on the other hand has an active layer supported by a larger layer with a greater pore size. The permeate can pass through the supporting layer much quicker than the active layer, so the process is superior overall in comparison to symmetric membranes.

An asymmetric membrane is commonly achieved in two ways. The membrane can be formed as a composite of multiple polymers which varies the porosity throughout the membrane, such as the thin film composite membrane in **Figure 1.12**.



**Figure 1.12:** Thin-film composite asymmetric membrane.

Alternatively, the membrane can gradually reduce in porosity by making the membrane form with a dense skin layer. **Figure 1.13** shows an example of a polysulfone skinned asymmetric membrane.



**Figure 1.13:** Skinned asymmetric membrane.

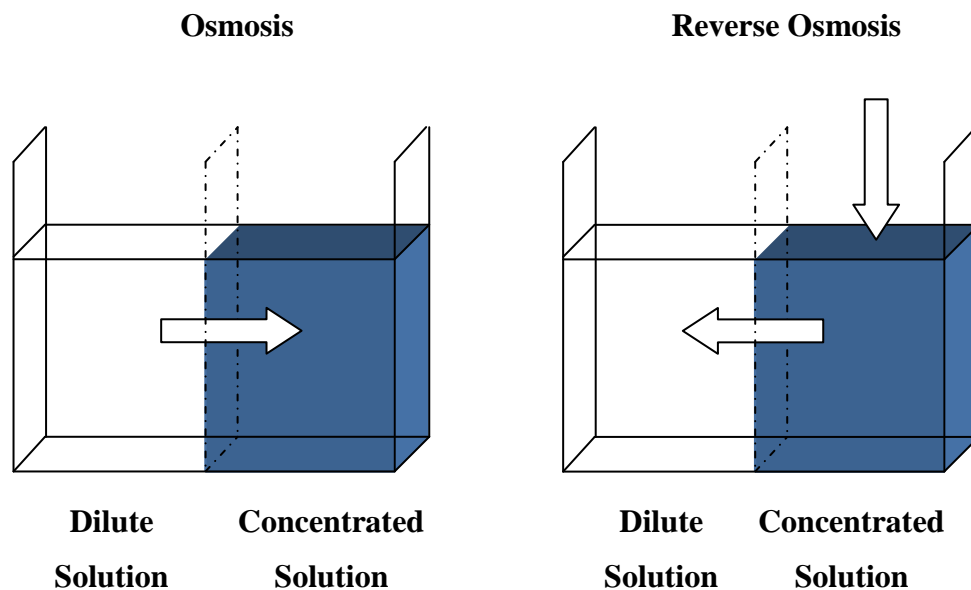


### 1.5.2 Types of Membrane Separation

There are a variety of different membrane separation processes which are available for different roles. By altering the material the membrane is made out of and the conditions of its manufacture, the pore size and pore density can be altered. Combined with various driving forces (pressure, electric current etc.) membranes can be customised for a range of purposes and are classified by what they can remove and by what process.

The most commonly used separation techniques are microfiltration and ultrafiltration which function like classical membranes. Microfiltration uses pore sizes between 10-0.05  $\mu\text{m}$ , usually symmetric type membranes and is used industrially to separate particles greater than 0.1  $\mu\text{m}$  in size from liquids. Ultrafiltration uses pore sizes between 0.05  $\mu\text{m}$ -1 nm, usually asymmetric type membranes and is used industrially to remove macromolecules from solution. The pores in ultrafiltration become so small that it is more sensible to categorise the membranes by molecular weight cut-off. This is the maximum size of molecules the pores will allow through, usually measured in Daltons, and for ultrafiltration it is around 1,000-50,000 Daltons.

Reverse Osmosis and Nanofiltration membranes have 100 Daltons and 200-1000 Daltons molecular weight cut off respectively. Due to the extremely small pore sizes they act as semi-permeable membranes rather than classical membranes. Both work in the opposite way to osmosis, the process which occurs commonly in biology (**Figure 1.14**).



**Figure 1.14:** Mode of action of reverse osmosis.

In reverse osmosis, an external pressure is applied to the concentrated solution which overcomes the osmotic pressure, forcing the aqueous from the concentrated side into the dilute side, further concentrating the concentrated solution, or purifying the aqueous depending on what you are trying to achieve.

This pressure driven transport requires pressures ranging from 100 psi in basic nanofiltration to over 1000 psi in some reverse osmosis setups, meaning the energy involved is higher than that of other filtrations.

There are many other types of membrane separation techniques tailored for specific needs and purposes as detailed in **Table 1.1**, which shows a general overview of membrane separation techniques.<sup>31</sup>

| Membrane Separation   | Membrane Type   | Driving Force                                | Applications   |
|-----------------------|---|--|--|
| Microfiltration       | Symmetric microporous                                 | Hydrostatic pressure                         | Sterile Filtration   |
| Ultrafiltration       | Asymmetric microporous                                | Hydrostatic pressure                         | Separation of macromolecular solutions                             |
| Nanofiltration        | Asymmetric microporous                                | Hydrostatic pressure                         | Separation of small organic compounds and salts from solution      |
| Hyperfiltration       | Asymmetric or composite with homogenous skin          | Hydrostatic pressure                         | Separation of microsolutes and salts from solution                 |
| Gas Permeation        | Asymmetric or composite, homogenous or porous polymer | Hydrostatic pressure, concentration gradient | Separation of gas mixtures   |
| Dialysis              | Symmetric microporous                                 | Concentration gradient                       | Separation of microsolutes and salts from macromolecular solutions |
| Pervaporation         | Asymmetric, composite                                 | Concentration gradient, vapour pressure      | Separation of mixture volatile liquids                             |
| Vapour Permeation     | Composite   | Concentration gradient                       | Separation of volatile vapours and gases                           |
| Membrane Distillation | Microporous   | Temperature                                  | Separation of water from non-volatile solutes                      |
| Electrodialysis       | Ion-exchange, homogenous or microporous polymer       | Electrical potential                         | Separation of ions from water and non-ionic solutes                |
| Electro-osmosis       | Microporous charged membrane                          | Electrical potential                         | Dewatering of solutions suspended solids                           |
| Electrophoresis       | Microfiltration membranes                             | Electrical potential, hydrostatic pressure   | Separation of water and ions from colloidal solutions              |
| Liquid Membrane       | Microporous, liquid carrier                           | Concentration, reaction                      | Separation of ion solutes from aqueous solutions                   |

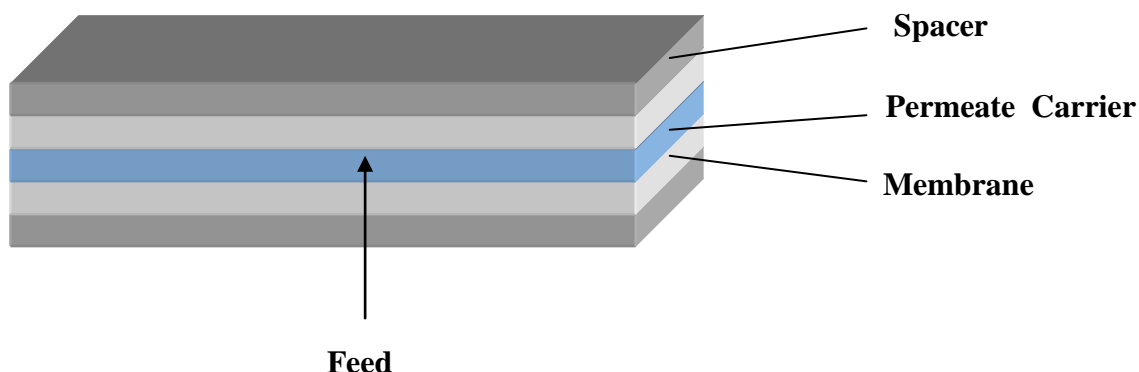
Table 1.1: General overview of membrane separation techniques.

### 1.5.3 Types of Module

Another factor in the type of membrane is how the membrane is packed, known as its module type. Whilst the pore size and whether the membrane is symmetric or asymmetric affects what is filtered and the efficiency, the way in which the membrane is set up for the separation effects the speed of the filtration, the membranes lifetime and the amount of membrane needed to filter a certain amount of material (the packing density).

#### 1.5.3.1 Plate and Frame Module

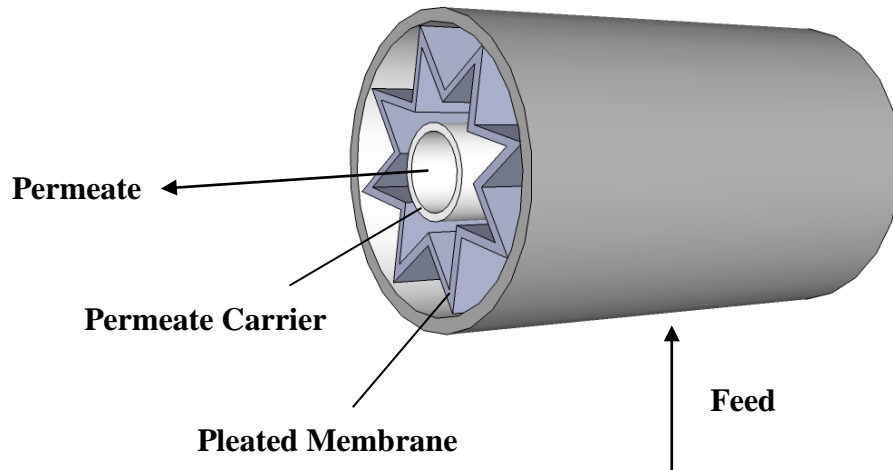
Plate and frame modules consist of two flat membranes bolted together, with the active layers facing outwards (**Figure 1.15**). They have a packing density of around  $100\text{--}400\text{ m}^2\cdot\text{m}^{-3}$ . The low packing density means that they are not considered “efficient” in comparison to other module types and as such are expensive to run and not commonly used.



**Figure 1.15:** Plate and frame module.

#### 1.5.3.2 Membrane Cartridge Module

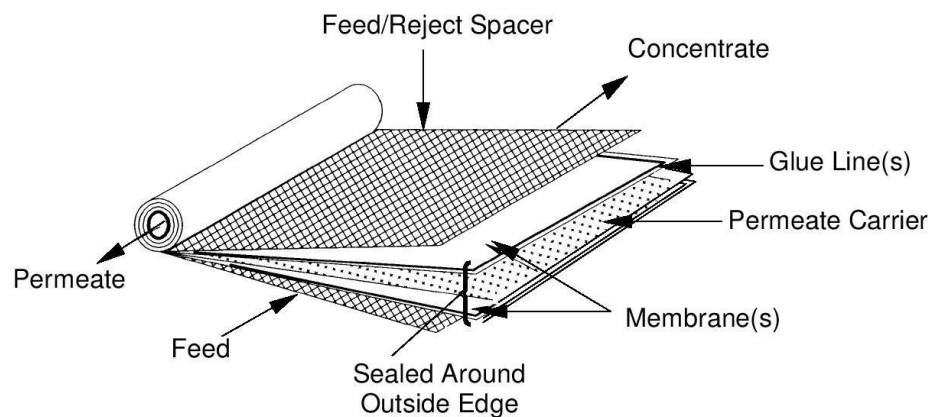
Membrane cartridge modules are a modification of the plate and frame module. As shown in **Figure 1.16** the flat sheets are folded and pleated to increase the packing density. These are encased to make a cartridge, which becomes modular and disposable.



**Figure 1.16:** Membrane cartridge module.

### 1.5.3.3 Spiral Wound Module

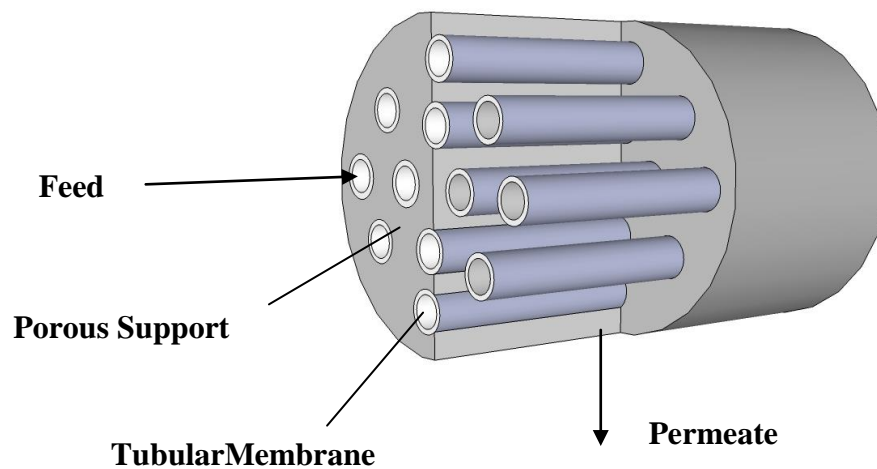
Spiral wound modules consist of membranes similar to the plate and frame module, wrapped around a central tube, where the permeate is removed (**Figure 1.17**)<sup>30</sup>. The feed flows through the plates, parallel to the tube, with the permeate dropping through the plate into the tube, in classic cross-flow manner. The non-permeating solute continues through the permeate carrier and is removed. By using multiple plates (multi-envelope system) the pressure of the system is kept high. The major advantage of this over the plate and frame module is its compact nature, with the packing density being around  $300\text{-}1000\text{ m}^2\cdot\text{m}^{-3}$ .



**Figure 1.17:** Spiral wound module.

#### 1.5.3.4 Tubular Membranes

Tubular membranes are asymmetric membranes in the form of tubes to increase the surface area per unit volume. **Figure 1.18** shows an exploded view of a tubular membrane where the tubular membranes (active layer) are embedded in a porous support layer. The feed passes through the middle of the tubes and the permeate passes out through the support layer. The packing density is however, still relatively low ( $300 \text{ m}^2 \cdot \text{m}^{-3}$ ) and the membranes are expensive and brittle.



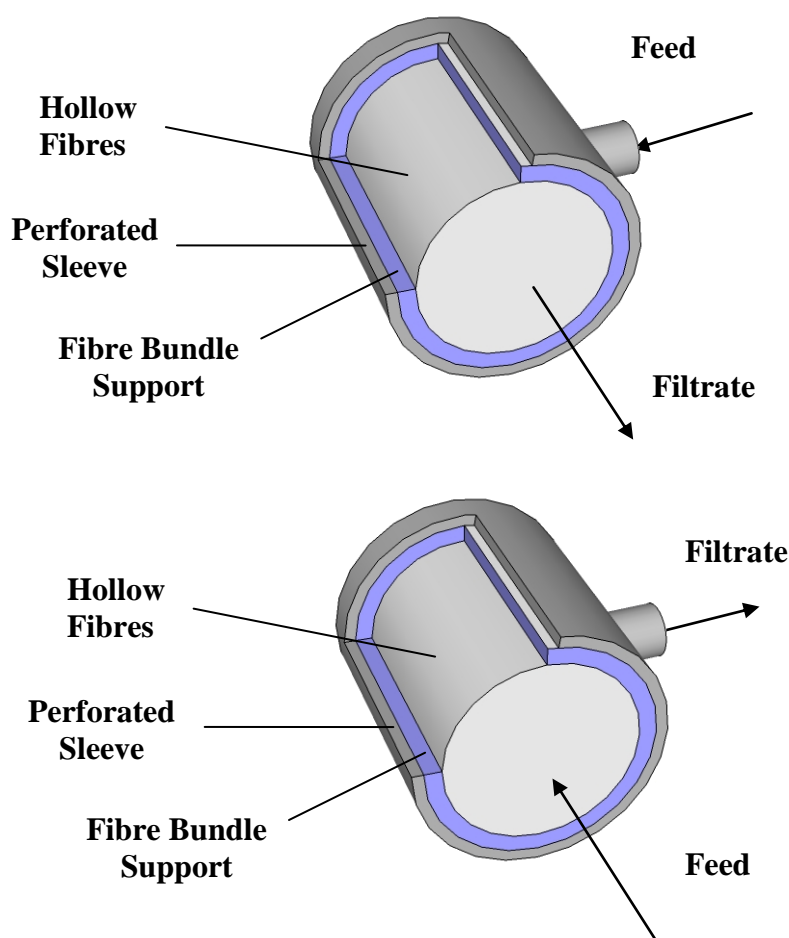
**Figure 1.18:** Tubular membranes.

#### 1.5.3.5 Capillary Membranes

Capillary membranes are smaller, much more efficient versions of tubular membranes. The membranes are arranged with their bottom parts sealed, similar in effect to a “dead-end” membrane. They can then operate either by the feed permeating through the membrane walls and the permeate being removed up through the fibre, or the feed passing down through the fibre with the permeate being removed through the walls. Both allow fouling to be considerably reduced.

## 1.6 Hollow Fibre Membranes

Hollow fibre membranes are similar to capillary and tubular membranes, but work on a much smaller scale. However, compared to capillary and tubular membranes, hollow fibre membranes have a very large packing density, upwards of  $30,000 \text{ m}^2.\text{m}^{-3}$ . Because of this, they are the most commonly used membrane. They can be used both with the feed or the filtrate permeating through the walls as shown in **Figure 1.19**.



**Figure 1.19:** Hollow fibre membrane bundles.

### 1.6.1 Hollow Fibre Synthesis<sup>32</sup>

One of the major advantages of hollow fibres over other membranes is in their synthesis; both the method of synthesis and the material used.

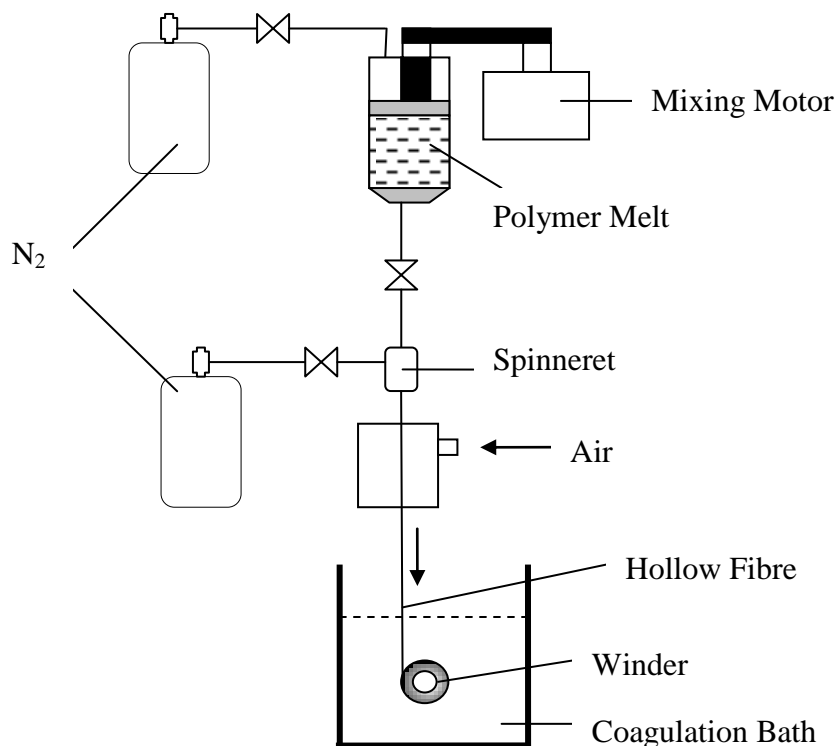
Hollow fibres are typical asymmetric membranes, with a dense top skin supported by a porous supporting layer. Unlike a number of asymmetric membranes however, they are almost always single material. The asymmetry of the membrane arises from the same material in different states, rather than a combination of two materials of varying porosity. The asymmetry is controlled by the manufacture of the membranes, which simplifies the manufacture somewhat and also greatly increases the range of materials they can be made from.

There are two main types of hollow fibre synthesis: **melt spinning** and **dry-wet spinning**. Both utilise different methods to control fibre synthesis and pore size.

### 1.6.1.1 Melt Spinning

The majority of commercially available fibres made from melt spinning are made *via* TIPS Melt Spinning (thermally induced phase separation).<sup>33</sup> **Figure 1.20** details a schematic of the hollow fibre melt spinning process. Typically, a polymer such as polypropylene or polyethylene is melted with an additive such as hydrocarbon oils (e.g. hexane)<sup>34</sup> or long chain fatty acids (e.g. oleic acid).<sup>35</sup> The additives are required to be able to form a good mixture with the polymer when heated (i.e. the melt). The heated melt solution is then passed through a spinneret to give it shape. As this is happening the solution begins to cool and the subsequent thermodynamic instability begins to separate the melt into two liquid phases (liquid-liquid phase separation), one of high polymer, low additive concentration and one of low polymer, high additive concentration. This is followed by the polymer reaching its freezing point, where it starts to solidify (solid-liquid phase separation) around the remaining additive/polymer mix which starts to form droplets. The coagulation bath is filled with a solvent the polymer is insoluble in to increase polymer precipitation; usually water. Therefore, when the polymer stream hits the coagulation bath, its freezing increases and traps the droplets to form a porous structure whilst also forming the dense top skin needed for the asymmetry of the membrane. Finally, the newly formed polymer is wrapped around a winder, which collects the fibre as well as stretching it, to further create more pores *via* microtears and cleavage of the polymer.





**Figure 1.20:** Schematic of hollow fibre melt spinning process.

The porosity of the fibre is determined by how the phase transition takes place and this depends on numerous factors: the temperature of the initial melt, the speed of spinning (controlled by the nitrogen pressure and the winder speed), the amount of time spent exposed to the air (related to the speed), the solubility of the polymer in the additive and the temperature and type of coagulant.

For example, the lower the temperature of the coagulation bath, the quicker solid-liquid transition occurs (the freezing). This impairs the liquid-liquid transition, and as such, the droplet formation and thus the micropore formation is retarded. As the coagulant temperature is increased the liquid-liquid and the solid-liquid transitions are impaired, again, impairing the micropore formation.

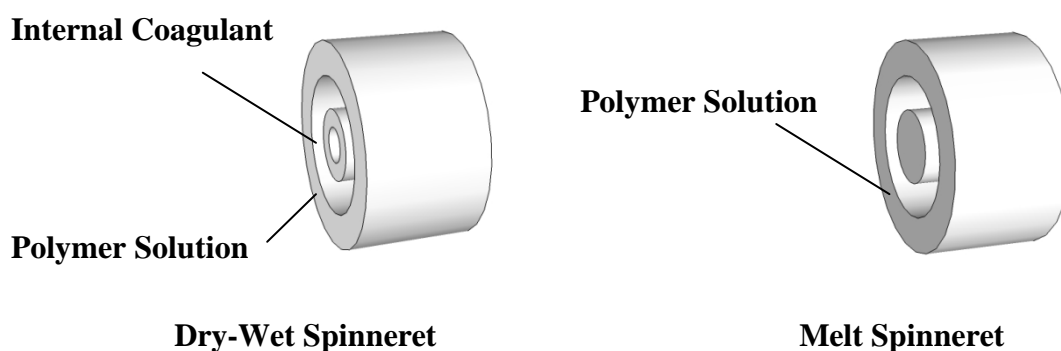
There are also a number of post-spinning treatments that alter the porosity of the fibres. Similarly to spinning, stretching of the fibres after the fibres have been spun, known as cold-stretching, can create micropores *via* stretching and cleaving of the polymer.

Another common post-spinning treatment is leaching components out of the polymer. By adding insoluble material to the polymer melt before spinning, the polymer can solidify around them during the freezing stage. After spinning, the fibres are then treated to remove these insoluble particles, thus leaving vacancies where the polymer formed around them, increasing the porosity. For example, a non-porous hollow fibre formed from polypropylene with a calcium oxide additive was treated with acid to remove the calcium oxide, resulting in a microporous hollow fibre.

### 1.6.1.2 Dry-Wet Spinning

Dry-Wet spinning is by far the most common way of producing hollow fibre membranes and shares many similarities with melt spinning. Whilst melt spinning is mainly achieved *via* TIPS, where the formation is controlled thermally, dry-wet spinning proceeds *via* non-solvent (or coagulant) induced phase separation (NIPS), where the fibre formation is controlled by the non-solvent.

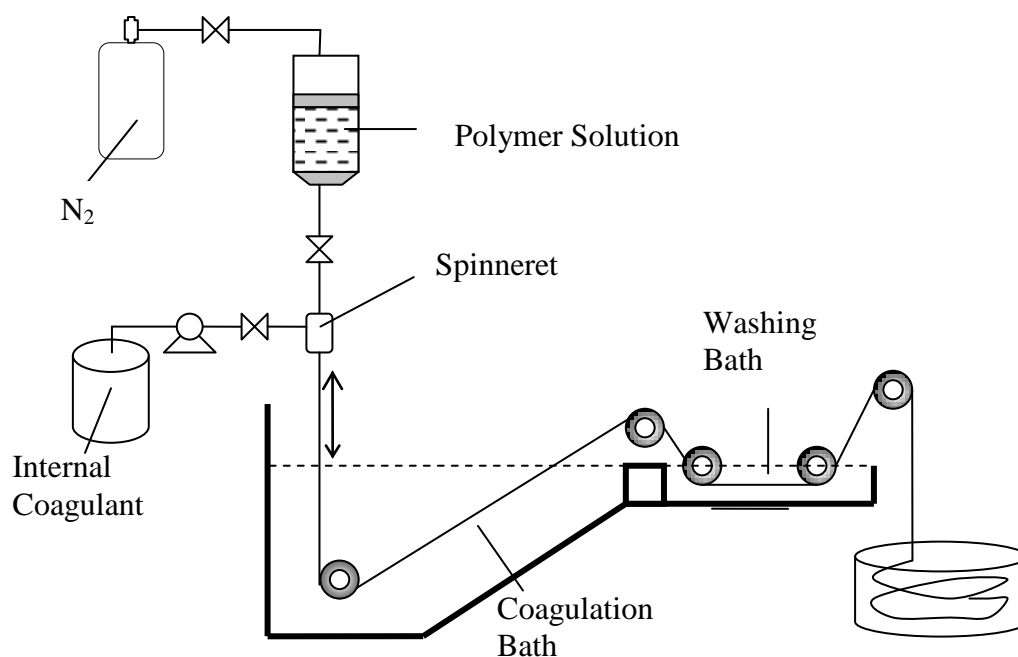
A schematic for fibre formation by dry-wet spinning is shown in **Figure 1.22**. A polymer such as polysulfone (PSF) or polyethersulfone (PES) is initially dissolved in a solvent that is highly miscible with water, such as dimethylsulfoxide (DMSO), acetone or *N*-methylpyrrolidone (NMP). The mixture is then passed through a spinneret, which differs from the melt spinning spinnerets as shown in **Figure 1.21**.



**Figure 1.21:** Cross-section of dry-wet and melt spinnerets.

In the dry-wet approach, a stream of non-solvent (usually the same as in the coagulation bath) is streamed down the centre of the polymer solution as it passes through the spinneret. This causes the solvent to dissolve in the non-solvent, precipitating the polymer in contact with it. The stream is then lowered into the coagulation bath, where the outside of the stream precipitates to form the fibre. The difference in coagulation between the inner and outer layers forms the asymmetry in the fibre and is responsible for forming a porous fibre.

As with melt spinning, there are a large number of variables effecting the fibre formation: type of solvent (how well the polymer dissolves and how well it mixes with water), type and temperature of non-solvent (coagulant), time exposed to atmosphere (the size of the air gap) and the speed at which the fibre is spun. For example, if the fibre is spun too fast, the polymer will precipitate very quickly. This makes the fibre very dense with a non-permeable skin layer.



**Figure 1.22:** Schematic of hollow fibre dry-wet spinning process.

There are also numerous methods of pre and post treatment that can change the properties of the fibre.

One such example is post treatment with chemicals to increase pore size. PSF is very hydrophobic and as such the flux of water passing through PSF fibres can be lower than desired. Mixing PSF with polyvinylpyrrolidone (PVP) gives a fibre which is more hydrophilic than a pure PSF fibre. It was found that treating the generated fibre with sodium hypochlorite (NaClO) increased the pore size and porosity of the fibre owing to NaClO partially eliminating PVP from the fibre. This degradation opens pores and creates new ones.<sup>36</sup>

Addition of silica to the polymer solution prior to spinning also achieves the same goal. The silica is removed post spinning to leave behind vacancies.

### 1.6.2 Hollow Fibre Applications<sup>32</sup>

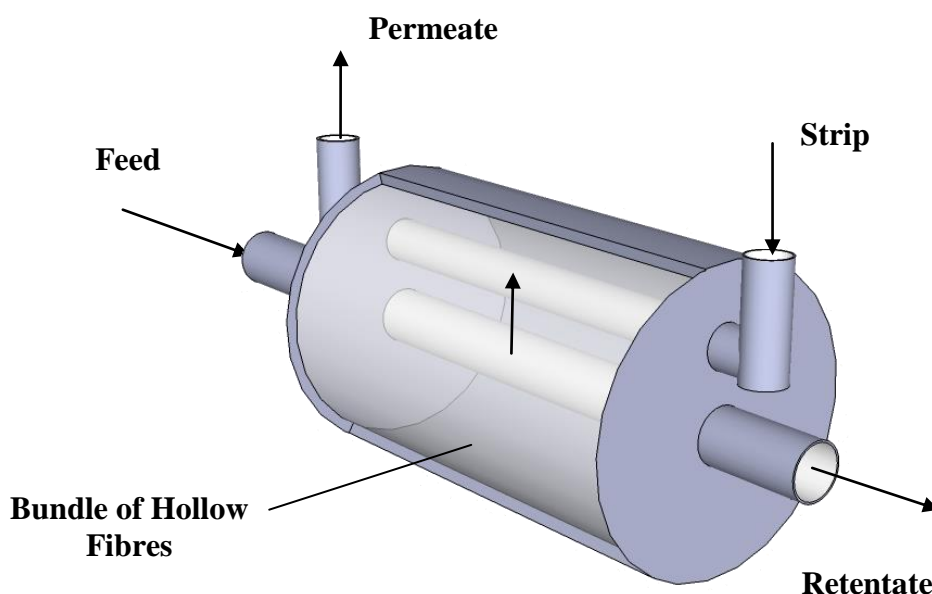
One of the great strengths of hollow fibre membranes is the ability to modify them for specific separations. Whilst the synthesis of the fibres and the resultant pore size and porosity is a big factor, how the finished fibres are utilised also plays a major part. Applications include haemodialysis membranes (artificial kidneys), pervaporation (e.g. dehydration), standard ultrafiltration/microfiltration and gas separation. The most interesting applications and those with the biggest scope for development, are membrane contactors and supported liquid membranes.

### 1.6.3 Membrane Contactors<sup>37</sup>

Membrane contactors separate gas-liquid and liquid-liquid systems without mixing or causing separation of the phases. The ability to remove an impurity from a substance without bringing it into contact with anything directly is highly desirable.

Hollow fibre membrane contactors consist of a bundle of hollow fibres packed together in a standard module. A cross-section of a hollow fibre membrane contactor is shown in **Figure 1.23**. Unlike a standard feed/retentate/permeate system, the contactors involve two flows of material on either side of the membranes; a feed flow containing the target

material, and a strip flow, consisting of solvent in which the material can dissolve. These two streams never come into contact, but the target material is allowed to permeate through the fibre walls between the streams. This effectively transfers the material from the feed flow to the strip flow under a concentration driven transport. A small pressure is applied to make sure the phases don't mix and the effective interface remains at the mouth of the pores.



**Figure 1.23:** Cross-section of hollow fibre membrane contactor.

Unlike most basic hollow fibre systems, the separation afforded by the contactor is granted by the choice of solvents rather than the pore size and porosity of the fibres. This means the specificity can be afforded by changing the solvents and pressures involved rather than having to develop new fibres for different purposes.

The separation of the phases prevents emulsification of the liquids which would impair separation and also allows the two flows to run at very high or very low rates without flooding or unloading of material.

Contactors are ideal for use in systems where the continuous removal of material is beneficial. For example, removing a product from a reaction to change the position of the equilibrium.

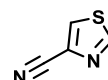
Hollow fibre contactors have been applied to a variety of separations including liquid-liquid extraction, gas-liquid extraction and chiral resolution.

### 1.6.3.1 Liquid-Liquid Extraction

An early working example of a liquid-liquid extraction using a hollow fibre contactor is the work by Prasad and Sirkar, who attached a contactor to a Merck process stream<sup>38</sup>. Using polypropylene fibres and a toluene or benzene strip flow, they managed to separate 4-methylthiazole **1.30** and 4-cyanothiazole **1.31** selectively from the aqueous feed.

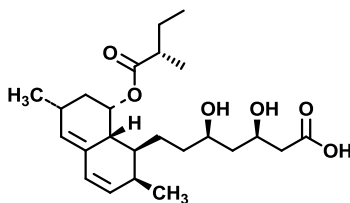


**1.30**

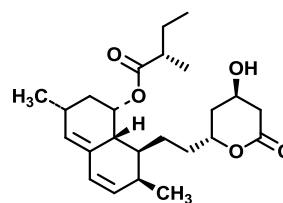


**1.31**

This technique was also applied to the separation of mevinolinic acid **1.32** into isopropyl alcohol from a production stream of mevinolin **1.33**.<sup>38,39</sup>



**1.32**

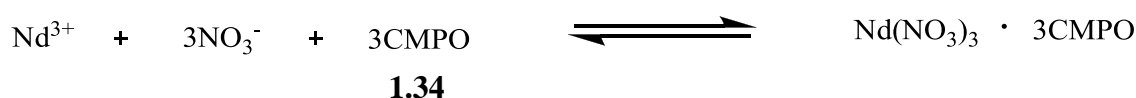


**1.33**

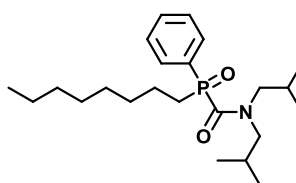
Another major area where liquid-liquid extraction is utilised is in the treatment of waste products. For example, phenol, a pollutant in water, was successfully extracted from water into a strip flow of methyl isobutyl ketone.<sup>40,41</sup>

In a different mode of action, water contaminated with trichloroethylene (a typical chlorinated pollutant) was purified *via* a polypropylene contactor bioreactor. The strip solution contained *Methylosinus trichosporium* OB3b bacteria which is methanotrophic and metabolises methane. These bacteria broke down the trichloroethylene as it entered the strip solution, successfully removing up to 99.99% of it from the aqueous feed.<sup>42</sup>

Heavy metals are another common pollutant that it would be useful to remove from water, due to their strongly toxic effects as well as the ability to recycle expensive metal catalysts. It was shown that neodymium (a surrogate for radioactive americium) could be extracted from aqueous media into a strip flow containing: 2M nitric acid, diisopropyl benzene and compounds such as *n*-octyl(phenyl)-*N,N*-diisobutylcarbamoylmethylphosphine oxide (CMPO) **1.34**. CMPO is an organic compound with an affinity for actinides that forms a complex with the neodymium to remove it into the strip flow (**Scheme 1.6**).



**Scheme 1.6**



**1.34**

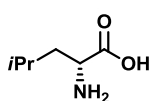
The neodymium can then be regenerated by passing it through another contactor, or backflowing it through the same contactor, into a 0.01M nitric acid solution.<sup>43</sup>

### 1.6.3.2 Gas-Liquid Extraction

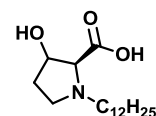
Gas-liquid extraction is currently used industrially to remove or trap gaseous impurities. A major example, which is an important topic, is the removal and trapping of the greenhouse gas CO<sub>2</sub> to prevent its release into the atmosphere. Hollow fibre contactors have been shown to adequately absorb CO<sub>2</sub> into aqueous strip solutions ideally to separate it from the other components of gaseous waste.<sup>44</sup>

### 1.6.3.3 Chiral Resolution

It has been shown that racemic mixtures can be separated by using a membrane contactor in conjunction with a chiral strip solution. The first example of this was the selective extraction of D-leucine **1.35** using a strip solution of octanol and *N*-*n*-dodecyl-L-hydroxyproline **1.36**.<sup>45</sup>



**1.35**



**1.36**

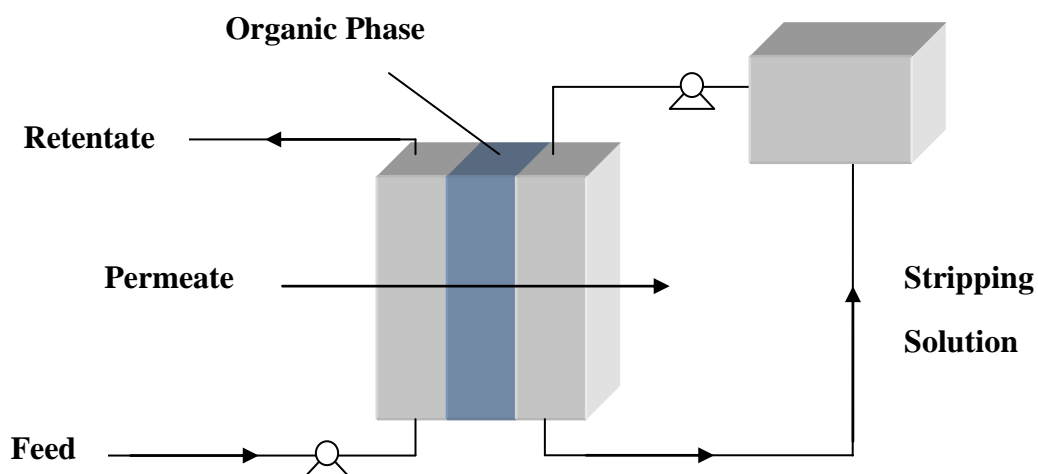
### 1.6.4 Supported Liquid Membranes<sup>46</sup>

Supported liquid membrane separation is similar in many ways to membrane contactors. However, the major difference is that there are three components rather than two in the separation; the feed solution, the strip solution and an organic phase embedded within the pores of the hollow fibres.

The setup is shown in **Figure 1.24**. The aqueous feed solution containing the separable material is passed on one side of a membrane while the strip solution is passed on the other. Unlike membrane contactors, the strip solution is aqueous. The phases are separated by the membrane which contains the organic layer, which usually consists of an organic solvent plus an extractant. The extractant is an additive which facilitates the passage of the target material from the feed, into the organic layer and then into the strip solution. As the



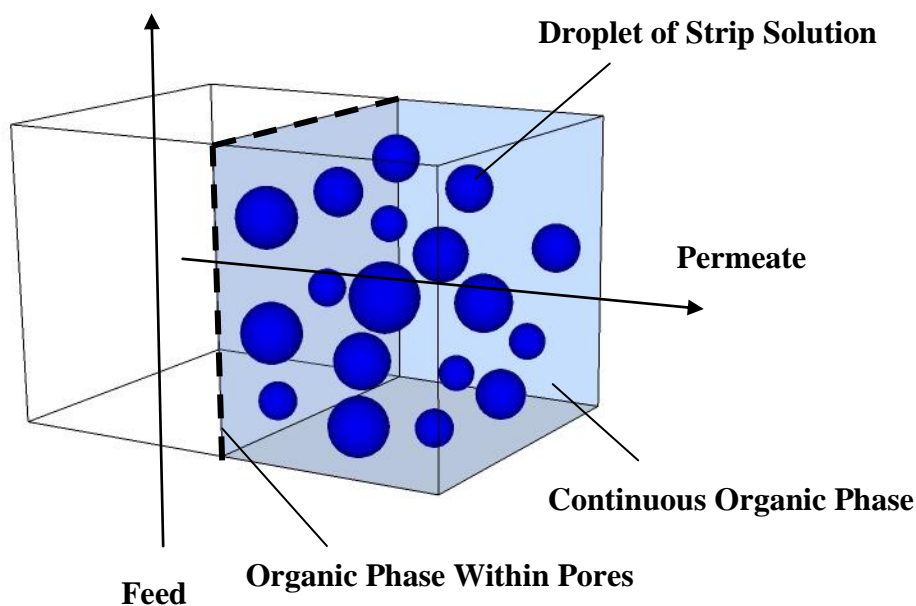
organic and aqueous phases are immiscible, the feed and strip can be controlled completely independently of each other.



**Figure 1.24:** Three-phase supported liquid membrane.

One problem found with these so called 3-phase SLM systems is that whilst the organic and aqueous phases are immiscible, emulsification can eventually occur, causing loss of the organic phase into the stripping solution. The force from the perpendicular flow of the stripping solution and the osmotic pressure through the membrane can end up forcing the organic layer from the pores. In this case the feed and strip solutions could end up mixing and the membrane failing.<sup>47,48</sup>

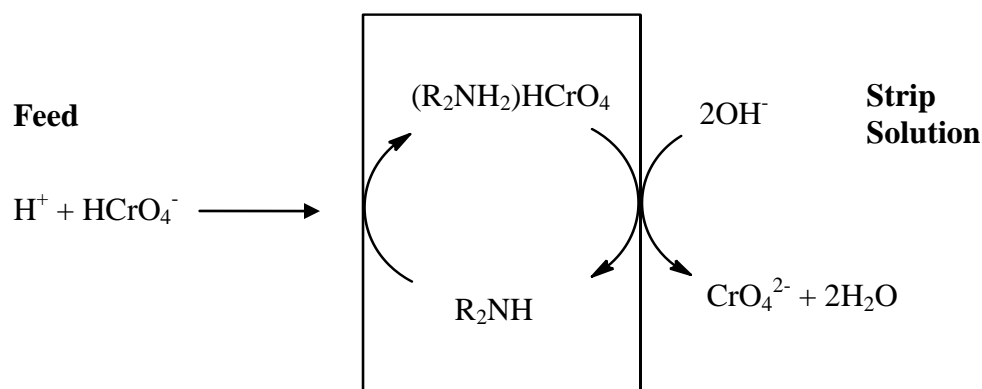
A solution to this problem came with using a 2-phase SLM system as shown in **Figure 1.25**. This involves dispersing the strip solution into an organic solvent to facilitate a continuous organic medium with aqueous droplets. The droplets formed tend to be around 80-800  $\mu\text{m}$  and considering the pore size of a standard polypropylene hollow fibre are in the magnitude of 0.03  $\mu\text{m}$ , the aqueous in the strip solution cannot pass through the membrane to mix with the feed. A small pressure is also applied on the feed side to prevent the organic phase leaking in the feed.<sup>49,50</sup> This added stability also results in added mass transfer due to the enhanced interface between the membrane layer and the strip solution.



**Figure 1.25:** Two-phase supported liquid membrane.

Similarly to membrane contractors, there are specific operations that the SLM systems have been applied to, of which environmental purposes seem to be foremost.

Removal of various metals from aqueous solutions using SLM hollow fibre systems is well documented. The removal of copper, chromium, strontium and zinc from waste water and the subsequent regeneration of them in concentrated amounts, has been shown with a standard SLM, specifying the organic phase to target the metals. An example of a chromium removal system (**Scheme 1.7**) consists of an organic membrane mixture of a *N*-lauryl-*N*-trialkylmethylamine (extractant, e.g. Amberlite LA-2), dodecanol (modifier) and PLURONIC L31 (polymer, helps phase separation) dissolved in Isopar L, with a stripping solution of sodium hydroxide.<sup>51</sup>



Scheme 1.7

The technique has also been applied as a quick purification process for analytical purposes, such as with blood testing and pollutant monitoring (**Figure 1.26**). The target analyte is separated from the feed into the strip solution via pipette, which can then be analysed directly. Drugs such as cocaine and cannabinol carboxylic acid, a component of cannabis, have been successfully separated directly from urine<sup>52,53</sup> and saliva<sup>54</sup> using a SLM. Even drugs such as amphetamines have been separated directly from blood and plasma.<sup>55</sup> Environmental pollutants such as organochlorine pesticides have been detected *via* this technique directly from soil samples.<sup>56</sup>

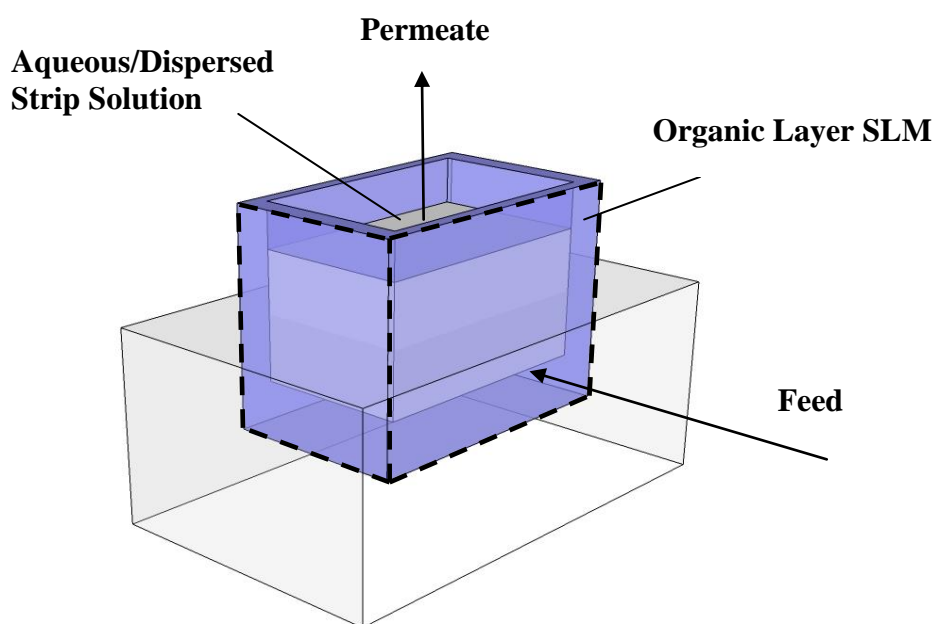


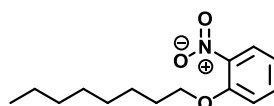
Figure 1.26: Supported liquid membrane for analytical testing.

### 1.6.5 Hollow Fibres in Sugar Separation

Whilst hollow fibres look suitable on paper for the task of separating oligosaccharides, there hasn't been a huge amount of work done in the area. It is clear that materials of the correct size can be separated from complex solutions such as blood and plasma, however, the specificity of separation is almost always based on size exclusion and thus could not distinguish between similar sized molecules.

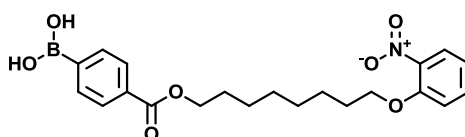
Luccio *et al.*<sup>57</sup> studied a system for the separation of fructose from glucose. Fermentation of sugar solutions of fructose and glucose into ethanol by certain strains of *Saccharomyces Cerevisiae* (yeast) leaves large amounts of fructose behind as only the glucose is fermented. The fructose can inhibit glucose fermentation at high concentrations so removal of fructose as it's produced would be ideal.

A hollow fibre SLM was tested with various quaternary ammonium salts (extractant) dissolved in 2-nitrophenyloctylether **1.37** (NPOE, organic solvent), but no fructose selectivity was achieved.



**1.37**

The system was then tried with a boronic acid, 4-[8-[(2-nitrophenoxy) octyloxycarbonyl]benzeneboronic acid **1.38**. This successfully resulted in separation of the sugars with 20 times the selectivity for fructose over glucose. This is especially interesting as fructose and glucose are isomers of each and therefore the separation is not size exclusion, but selectivity due to binding recognition.



**1.38**

## **1.7 Conclusion**

This chapter has given a brief introduction to the history and development of boronic acids as chemosensors, specifically for sugar detection. It also discussed a wide range of membrane separation techniques available, with emphasis on hollow fibre membranes and their potential for sugar separation.

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## **Chapter 2 : Boronic Acid Appended Polymers for Sensing and Separation**

### **2.1 Introduction**

As alluded to in Chapter 1, the detection, separation and purification of saccharides is an important task relevant to many issues such as diabetes, disease biomarkers and biofuels.

#### **2.1.1 Diabetes Blood Monitors**

Blood glucose levels are required to be regularly, accurately and quickly monitored at a scale and simplicity that can be operated by the general public. This necessitates the detection of glucose from within a complex blood mixture. Current home monitors are based on the glucose oxidase enzymatic system<sup>1</sup> which encounters problems with temperature, pH and interfering molecules such as ascorbates.<sup>2</sup> The need for a blood sample also makes these methods invasive. Chapter 1 has shown the extensive work undertaken with regards to boronic acid saccharide sensors, predominantly aimed at creating increasingly stable, accurate and even less invasive diabetes monitors.<sup>3</sup>

#### **2.1.2 Oligosaccharide Disease Biomarkers**

Specific oligosaccharides are generated by certain diseases such as cancer at an early stage in the disease, but are only present in low concentrations. Purification, followed by detection of these oligosaccharides from bulk samples, such as blood, could be used to diagnose the relevant disease earlier than is currently possible.<sup>4</sup> The aforementioned work by Yang *et al.*<sup>5</sup> shows the potential and scope for boronic acids in the identification of specific oligosaccharides. Various membrane systems can be made to reject or permeate oligosaccharide sized molecules and could be engineered to purify oligosaccharides from a bulk solution, but not selectively for specific oligosaccharides.



### 2.1.3 Natural Sugar Separation

The major sources of consumable sugar are various sucrose rich plants such as Sugar Beet or Sugar Cane, which can be processed into a mixture of glucose and fructose.<sup>6</sup> Separation of this mixture is conventionally difficult and usually requires expensive chromatographic techniques.<sup>7</sup> The basic application is for the production of higher concentration glucose or fructose, desirable for things such as high concentration fructose syrups as lower calorie sucrose supplements; fructose is much sweeter than sucrose so less is required.<sup>8</sup> Perhaps a more important application is for bioethanol, currently an important fuel source in countries such as Brazil and increasingly being looked to as an alternative to petroleum.<sup>9</sup> Generally, various strains of yeast ferment sucrose or other sugar mixtures into ethanol. In some cases, the presence of fructose or the produced ethanol within the broth inhibits fermentation<sup>10,11</sup> and as such, removal of these potential inhibitors would improve the process. Due to the near identical size of fructose and glucose, separation by traditional membranes is not possible. Boronic acids however, have shown an affinity for fructose over glucose, so their incorporation could facilitate the separation.<sup>8,10</sup>

## 2.2 Research Rationale and Aims

Looking at the cases of oligosaccharide and natural sugar separation, there is a running theme. The requirement is that a specific sugar is separated from either a bulk solution or from similar molecules.

Membranes are excellent at separating molecules of a certain molecular weight cut-off from bulk solution, but they cannot distinguish between molecules of similar size, meaning similar sized molecules such as fructose and glucose will remain together.

Boronic acids on the other hand can be tailored to show great selectivity and affinity for specific molecules, but have no inherent ability to separate them and can sometimes struggle to pick them out of complex solutions.

Combining the two methods into one system has achieved results neither could have separately. The most relevant example is the aforementioned work by Di Luccio and Smith<sup>10</sup> and the similar work of Duggan.<sup>12</sup> These show the combination of a boronic acid

compound as a fructose selective component, with a supported liquid membrane to facilitate the separation of a normally inseparable mixture of glucose and fructose.

### 2.2.1 Fructose Selectivity of Boronic Acids

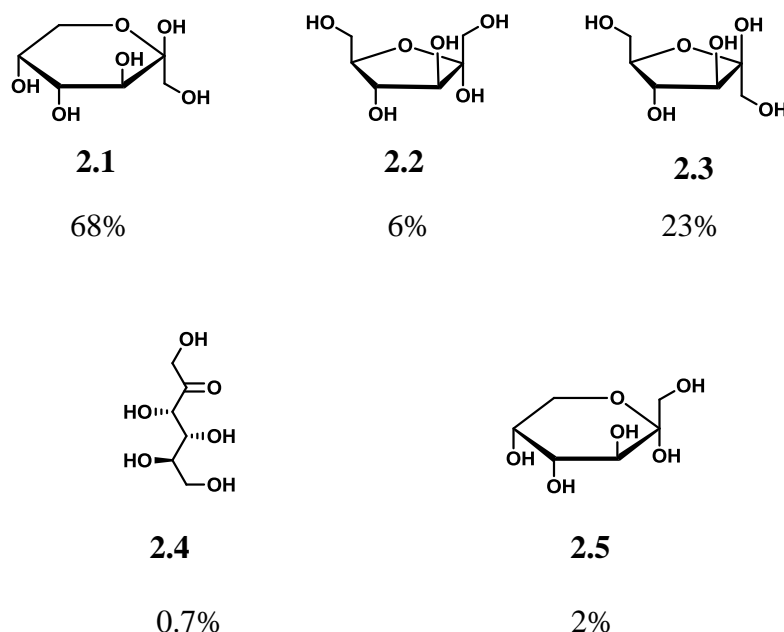
Arguably the most important aspect of the separation system is the ability to be selective. In the case of fructose, selectivity with boronic acids is easy to achieve since boronic acids are naturally selective for fructose over other sugars such as glucose and galactose. **Table 2.1** shows the binding constants of various polyols with phenylboronic acid in water.<sup>13</sup> The binding constant for D-fructose is 4400 K/mol<sup>-1</sup> which is significantly larger than for other sugars.

| Polyol                    | K/mol <sup>-1</sup> |
|---------------------------|---------------------|
| 1,3-propanediol           | 0.88                |
| ethylene glycol           | 2.80                |
| propylene glycol          | 3.80                |
| 3-methoxy-1,2-propanediol | 8.50                |
| D-glucose                 | 110                 |
| D-mannose                 | 170                 |
| D-galactose               | 280                 |
| Pentaerythritol           | 650                 |
| Mannitol                  | 2,300               |
| D-fructose                | 4,400               |
| Catechol                  | 18,000              |

**Table 2.1:** Binding constants of polyols with phenylboronic acid in water.

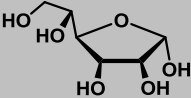
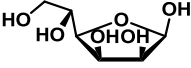
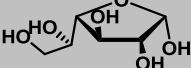
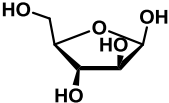
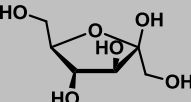
This can be explained statistically by looking at the various forms monosaccharides can take in aqueous media *via* isomerisation at the anomeric position. D-Fructose for example, exists in equilibria with its five forms (**Figure 2.1**);  $\beta$ -D-fructopyranose **2.1**,  $\beta$ -D-

fructofuranose **2.3**,  $\alpha$ -D-fructofuranose **2.2**,  $\alpha$ -D-fructopyranose **2.5** and acyclic fructose **2.4**.<sup>14</sup>



**Figure 2.1:** Hawthorn projections of fructose isomers.

Any of the five isomers will bind with a boronic acid in the usual fashion, with two adjacent hydroxyl groups forming five or six membered rings. However, as shown by the NMR and molecular modeling studies of Norrid<sup>14</sup> and Nicholls,<sup>15</sup> the optimum diol pair making the most stable boronic acid diol complex is a *syn*-diol at the anomeric position on a furanose ring. With regards to fructose, that would mean  $\beta$ -D-fructofuranose **2.3** possesses the diol pair to make the most stable boron complex. Assuming each monosaccharide has a form with a *syn*-diol at the anomeric position on a furanose ring which gives the most stable boron complex, then the relative concentration of that form will be related to the overall binding strength of the sugar. As such, the binding strengths of monosaccharides can be gauged by comparing the relative concentration of the most stable form (**Table 2.2**).<sup>16</sup>

| Saccharide                                 | Structure   | Relative Percentage of the Total Composition (in D <sub>2</sub> O) | K <sub>obs</sub> with Phenylboronic Acid / dm <sup>3</sup> mol <sup>-1</sup> |
|--|---|--|--|
| D-glucose ( $\alpha$ -D-glucofuranose)     |    | 0.14%  | 110  |
| D-mannose ( $\beta$ -D-mannofuranose)      |    | 0.3%   | 170  |
| D-galactose ( $\alpha$ -D-galactofuranose) |   | 2.5%   | 280  |
| D-arabinose ( $\beta$ -D-arabinofuranose)  |  | ~2%  | 340  |
| D-fructose ( $\beta$ -D-fructofuranose)    |  | 25%  | 4400   |

**Table 2.2:** Binding constant of phenylboronic acid with monosaccharides versus relative *syn*-diol concentration.

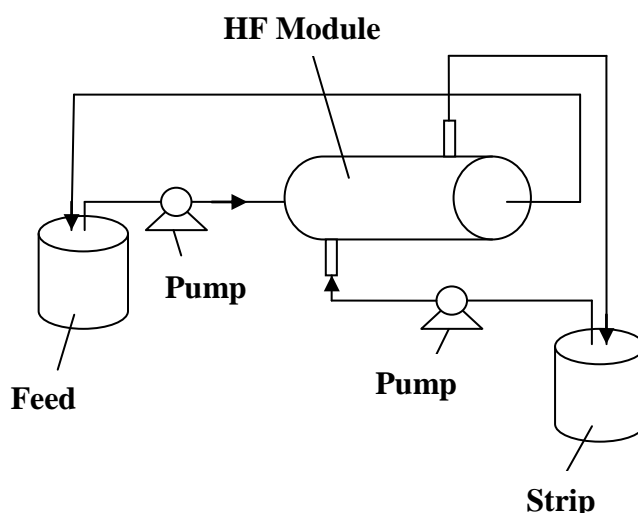
**Table 2.2** shows a range of monosaccharides in their optimum boronic acid binding forms versus the relative concentration of those forms in D<sub>2</sub>O at 31 °C<sup>17</sup> (in D<sub>2</sub>O at 27 °C in the case of glucose<sup>18</sup>). Comparatively, fructose has a much higher concentration of the optimum form, so it is unsurprising that it shows an overall higher binding affinity. This also fits with catechol's roughly four times higher binding affinity, as 100% of catechol has a *syn*-hydroxyl group pair.

### 2.2.2 Fructose Selective SLM

The Smith group initially explored the use of boronic acids as carriers for biomolecules such as glycosides<sup>19</sup> and nucleotides<sup>20</sup> through various membrane systems. This led to research into glucose transportation<sup>21</sup> and eventually fructose separation.<sup>8</sup>

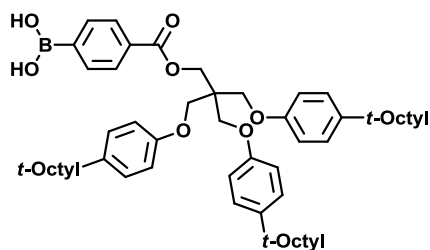
A Flat sheet SLM consisting of microporous polypropylene impregnated with 2-nitrophenoxyoctylether **1.36** and the carrier 4-[8-[(2-nitrophenoxy)octyloxycarbonyl]benzeneboronic acid **1.37**, gave up to a 14-fold selectivity for fructose extraction from a 50:50 glucose/fructose mixture.

The system was improved by switching to a Hollow Fibre SLM, to give up to a 20-fold selectivity for fructose.<sup>22</sup> Although the selectivity is improved whilst having much lower boronic acid concentration, the system has a reduced flux with respect to the flat sheet membrane. However, the necessity to stir the feed in a flat sheet system causes flow disturbance and sheer forces at the membrane surface which destabilises the membrane and causes emulsification.<sup>23</sup> The feed in a hollow fibre module (**Figure 2.2**) flows perpendicular to the permeate flow, greatly reducing these forces to improve membrane stability.



**Figure 2.2:** Schematic of hollow fibre supported liquid membrane separation system.

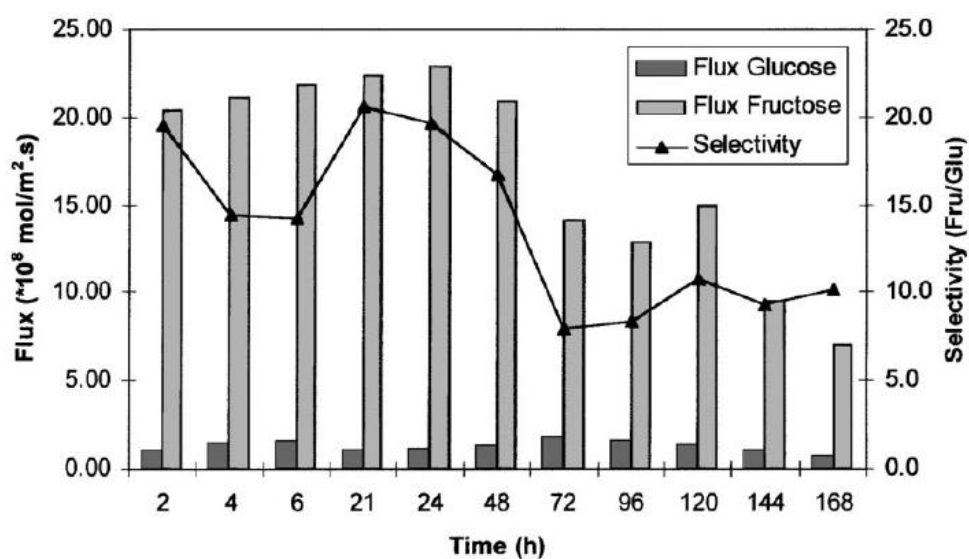
Duggan<sup>12</sup> proposed a similar system, using a highly lipophilic pentaerythritol based boronic acid carrier **2.6** to achieve an 8:1 fructose selectivity over glucose.



**2.6**

### 2.2.3 Problems and Possible Solutions

Hollow Fibre SLMs, whilst an improvement on Flat Sheet SLMs, still have problems with regards to stability and degradation of the membrane, especially over protracted periods of use.<sup>24</sup> Long term efficiency of the membranes was investigated (**Figure 2.3**),<sup>22</sup> finding that flux and selectivity greatly suffered over time, due to suspected leaching of the carrier into the aqueous layer.



**Figure 2.3:** Flux and selectivity of hollow fibre supported liquid membranes versus time.

An alternative to supported liquid membranes would be to use fixed carrier membranes (FCM). In these solid state membranes, the carrier is covalently bound or anchored within the polymer backbone. The fixed nature of the carriers imparts great stability onto the membranes, as they cannot suffer from the leeching and emulsification problems SLMs have.

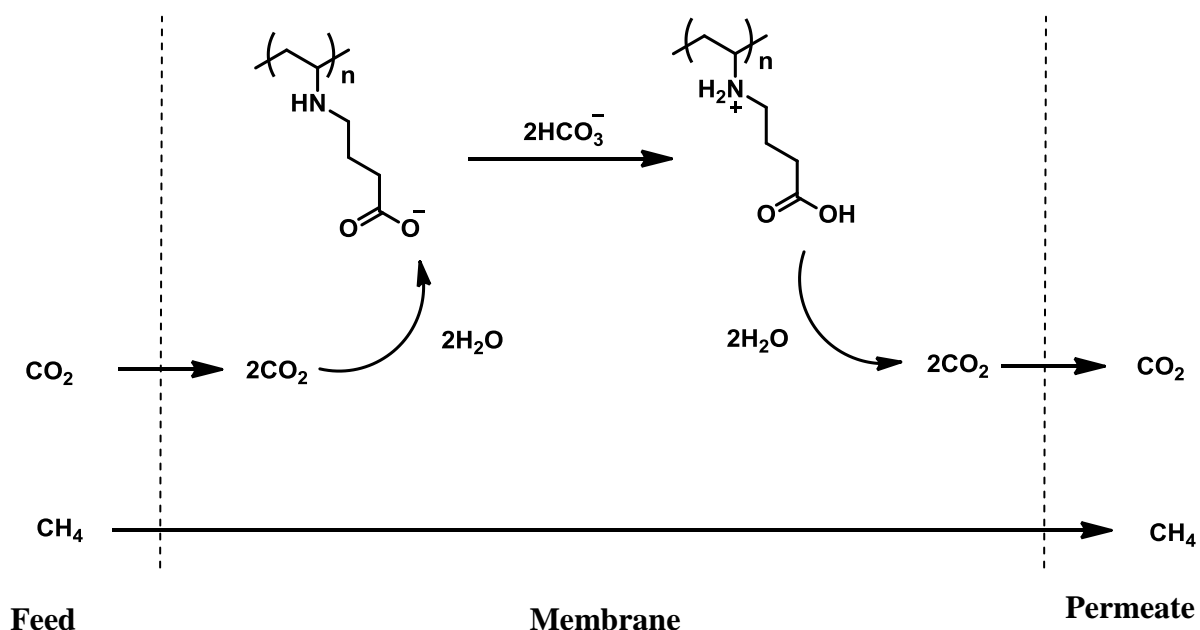
### 2.2.4 Fixed Carrier Membranes

FCMs generally work through two possible mechanisms; carrier diffusion or fixed-site jumping.

#### 2.2.4.1 Carrier Diffusion

The carrier reacts reversibly with a compound within the feed, converting it into a form which permeates at a different rate to the remaining feed and then regenerates the initial compound upon exiting the membrane. This is mainly the case in gas separation membranes, specifically in the separation of CO<sub>2</sub> from neutral gases such as CH<sub>4</sub>,<sup>25</sup> H<sub>2</sub>,<sup>26</sup> and N<sub>2</sub>.<sup>27</sup>

For example, Zhang *et al.*<sup>28</sup> designed a hydrolysed polyvinylpyrrolidone (PVP) membrane that gave up to a 200-fold selectivity for CO<sub>2</sub> over CH<sub>4</sub>. When the gas feedstock was passed through the water swelled membrane, the CO<sub>2</sub> reacted with the PVP to form bicarbonate ions (**Figure 2.4**). These ions travel quickly through the membrane and are then regenerated as CO<sub>2</sub> upon exiting. The CH<sub>4</sub> is unreactive to the membrane so permeates through a much slower solution-diffusion process. As such, the flux of CO<sub>2</sub> through the membrane is much greater than that for CH<sub>4</sub>, causing the selectivity.



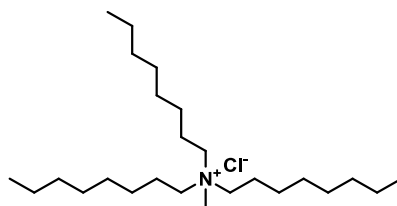
**Figure 2.4:** Mode of action of carrier diffusion gas separation membrane.

#### 2.2.4.2 Fixed-Site Jumping

The carriers act as stepping-stones for the transported substances. This can be facilitated either by limited diffusion of chained carriers<sup>29</sup> (the carriers are attached to the polymer backbone by a flexible chain, allowing them to “pass” the solute between themselves) or by segmental motion<sup>30</sup> (swelling/rotation/movement of the main polymer chain containing the carrier sites). Alternatively, the polymer contains sites which rather than increasing the diffusion of a solute, cause separation by retarding the diffusion of another.<sup>31</sup> Membranes of this type have been used to separate various metal ion mixtures,<sup>32,33</sup> non-functional mixtures such as benzene/cyclohexane<sup>31</sup> and functional molecules such as carbohydrates<sup>34</sup> and amino acids.<sup>35</sup>

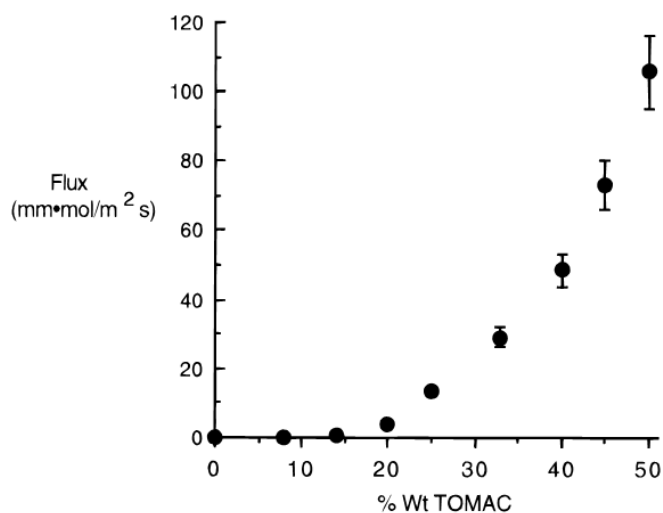
An example of sugar separation by anion exchange membranes used a plasticised cellulose triacetate membrane impregnated with 2-nitrophenyloctyl ether **1.36** and trioctylmethylammonium chloride **2.7** (TOMAC) as the carrier.<sup>36</sup>





2.7

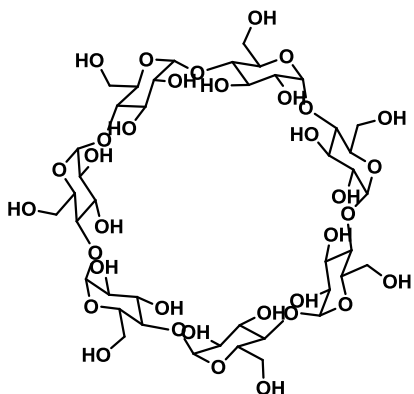
Smith *et al.*<sup>34</sup> found that when the concentration of TOMAC became high enough, the membranes would permeate small monosaccharides, with a twofold selectivity for fructose over glucose. Interestingly, this indicates that the membrane works *via* fixed-site jumping rather than carrier diffusion. For a carrier diffusion system, the flux of permeate should increase linearly with concentration of carrier. In a fixed-site jumping system, it is postulated that there is a minimum concentration of carrier required, relating to the maximum distance between carriers to allow the solute to jump between them. This is known as the percolation threshold. Below the threshold, flux is negligible as the carriers are too far apart, above the threshold fixed-site jumping can occur and the flux increases rapidly, as shown in **Figure 2.5**.<sup>34</sup>



**Figure 2.5:** Flux of monosaccharides versus TOMAC concentration.

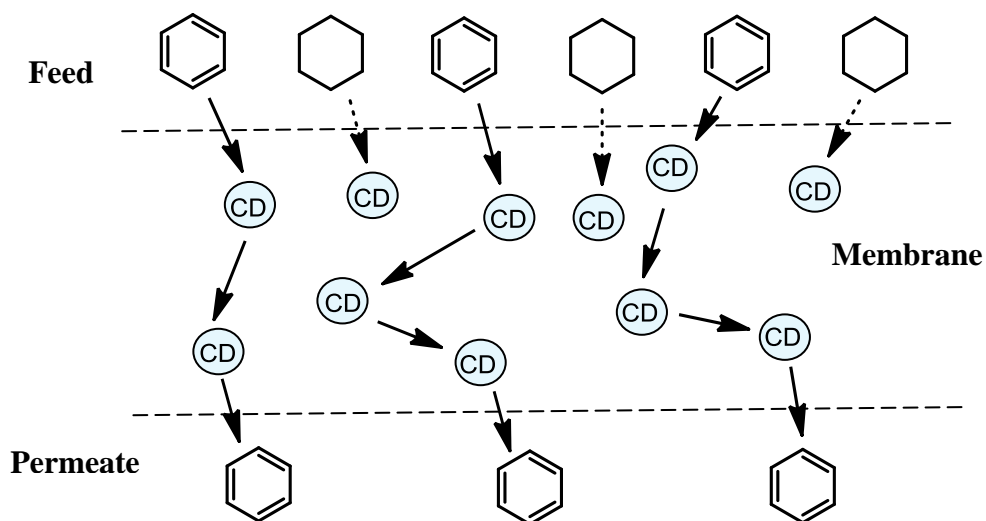
For the benzene/cyclohexane separation,<sup>31</sup> a polyvinyl alcohol membrane was prepared containing  $\beta$ -cyclodextrin **2.8** as the fixed carrier, to give up to a 30-fold selectivity

towards benzene. Cyclodextrin (CD) contains a lipophilic pocket so it can form inclusion complexes with both benzene and cyclohexane.



## 2.8

The complex of CD with cyclohexane is much stronger than with benzene, so the fixed-site jumping from one CD to another occurs more rapidly for benzene, as it is less strongly bound. As such, benzene permeates the membrane much faster than cyclohexane, separating the mixture (**Figure 2.6**).



**Figure 2.6:** Mode of action of cyclodextrin based fixed carrier membrane.

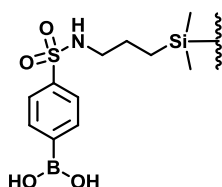
### 2.2.5 Boronic Acid Fixed Carrier Membrane

Fixed carrier membranes have been shown to be able to separate a number of compounds, including sugars. With the existence of boronic acid SLMs, it is not unreasonable to postulate that a membrane could be designed where the fixed carrier is a boronic acid and the target is some form of saccharide. It is unlikely that a boronic acid would support a carrier diffusion type membrane and there is no evidence of boronic acids being able to facilitate separation *via* a fixed-site jumping system leading to an increase in flux, at least with regards to saccharides. There is however, evidence pointing to the potential of boronic acids to act as fixed carriers imparting separation by retarding the progress of target analytes like sugars, such as Boronate Affinity Chromatography (BAC) or Boron Affinity Saccharide Electrophoresis (BASE).

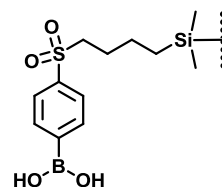
BAC consists of various chromatography systems where selectivity is enhanced by the interaction between mobile or solid phase boronic acids with *cis*-diol type compounds, such as saccharides. Separation of these compounds could not be facilitated by an equivalent non-boronic acid chromatography system.<sup>37</sup>

The solid phase appended boronic acids can be considered equivalent to a fixed carrier. Various boronic acid appended solid phases such as silica,<sup>38</sup> polymers<sup>39-42</sup> and gels,<sup>43-45</sup> have been used to separate a range of saccharide related compounds such as glycosylated proteins<sup>39,42-45</sup> (proteins with sugar residues) and nucleotides.<sup>38,40,41</sup>

Schöneich *et al.*<sup>38</sup> demonstrated the separation of a mixture of *cis*-diols using two boronic acid modified silica gels (**2.9**, **2.10**).

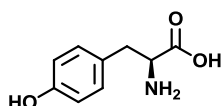
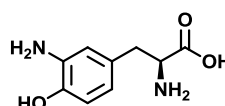
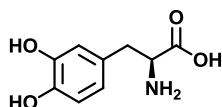
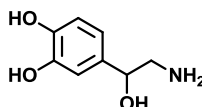
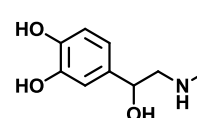


**2.9**



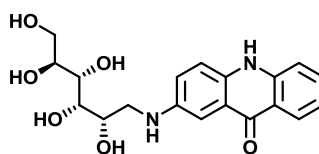
**2.10**

Under normal isocratic chromatographic conditions, a mixture of L-tyrosine **2.11**, 3-amino-L-tyrosine **2.12**, L-DOPA **2.13**, (-)-norepinephrine **2.14** and (-)-epinephrine **2.15** would elute as two co-elutions; L-tyrosine, 3-amino-L-tyrosine, L-DOPA as one elution and (-)-norepinephrine with (-)-epinephrine as another. When the modified silica was used, L-tyrosine and 3-amino-L-tyrosine still co-eluted, but the other 3 compounds were fully separated.

**2.11****2.12****2.13****2.14****2.15**

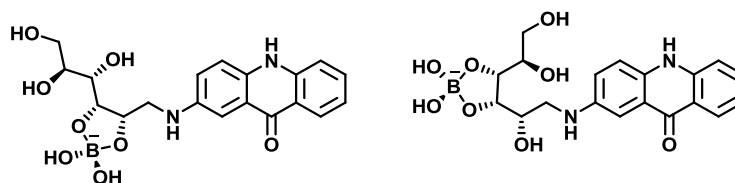
The L-tyrosine and 3-amino-L-tyrosine are co-eluted first as they do not have the *cis*-diol pair to interact with the boronic acid, and thus are only effected by normal chromatographic conditions. L-DOPA, which co-eluted when using regular silica, was fully separated from the very similar L-tyrosine and 3-amino-L-tyrosine using modified silica. This is due to L-DOPA having the necessary *cis*-diol to interact with the boronic acids and thus have its progress through the column retarded. It was also fully separated from both (-)-norepinephrine and (-)-epinephrine, two similar compounds containing *cis*-diols. This shows that the boronic acid modified silica columns are not acting as simple ion-exchange style columns where all similar analytes stick and are then washed off after being separated from the bulk. Instead, the boronic acid modified silica is a true chromatographic system with the ability to separate similar compounds by a polarity gradient.

BASE is similar to BAC, in that it is a boronic acid modified version of the existing separation system Fluorophore-Assisted Carbohydrate Electrophoresis (FACE). Gel electrophoresis is the separation of compounds by applying an electric field across a polymer gel matrix, causing separation of charged compounds added to the gel based on their size and their charge. FACE is a specialisation of the technique aimed at separating and visualising carbohydrate based compounds, such as saccharides or proteins with carbohydrate residues, using a polyacrylamide gel.<sup>46</sup> In the case of monosaccharides, they are labeled with the fluorophore 2-aminoacridone (AMAC) in order to visualise them, such as the glucose derivative **2.16**.



**2.16**

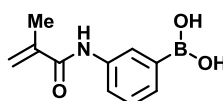
Boric acid is added to the electrophoresis buffer where it forms boronate ions, thus imparting a charge onto the otherwise neutral sugars, as shown in **Figure 2.7**.<sup>47</sup> In this case the boric acid is acting as a mobile carrier akin to the previously mentioned SLMs; without the boric acid present, the electrophoresis cannot occur.



**Figure 2.7:** Boronate ions of AMAC labelled glucose.

FACE is good at resolving a mixture of differently sized or charged compounds, but is poor at separating similar compounds, as their size to charge ratios will all be very similar.

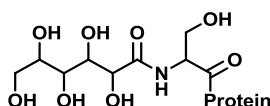
This is the case for compounds such as differing monosaccharides, which have near identical sizes. There is however marginal separation based on the difference in stability of the different possible boronate esters formed. BASE utilises the FACE system, but adds methacrylamido phenylboronic acid **2.17** to the acrylamide mixture when polymerising the gel to give a polymer matrix containing fixed boronic acid sites.<sup>48</sup>



**2.17**

The addition of the boronic acids imparts selectivity towards *cis*-diol compounds in keeping with previous examples. The fixed boronic acids bind to the compounds and retard their progress through the gel, imparting selectivity relative to the strength of the binding of the *cis*-diol to the boronic acid. Fossey *et al.*<sup>48</sup> demonstrated that the BASE system was able to cleanly separate a mixture of AMAC-labeled mono and disaccharides (lactose, galactose, N-acetyl glucosamine, melibiose and glucose) which was inseparable under normal FACE conditions, thus highlighting the selectivity afforded by the fixed boronic acids.

Van den Elsen *et al.*<sup>49</sup> investigated BASE as an improvement over the typical sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) used to separate proteins. Using the BASE conditions, referred to as methacrylamido phenylboronate acrylamide gel electrophoresis (mP-AGE), *Staphylococcus aureus* immune-subversion protein Sbi was successfully separated from its D-glucanolactone adduct **2.18**.



**2.18**

Due to the size of proteins, glycosylated and non-glycosylated versions of the same proteins are inseparable under normal SDS-PAGE conditions; the difference in weight is not great enough to allow resolution (16527.2 Da vs. 16705.2 Da).

When running mP-AGE, a molecular weight marker is used as a reference to give a rough idea of the molecular weight of the analytes. By comparing the position of the glycosylated protein with the marker, a “virtual” molecular weight can be given to it. This value is proportional to both the concentration of the boron in the gel, and the strength of the retention of the protein. In this case, the retardation by the boronic acids was equivalent to up to a four times increase in molecular weight of the protein, which gives a huge separation between the glycosylated and non-glycosylated proteins.

### 2.3 Design

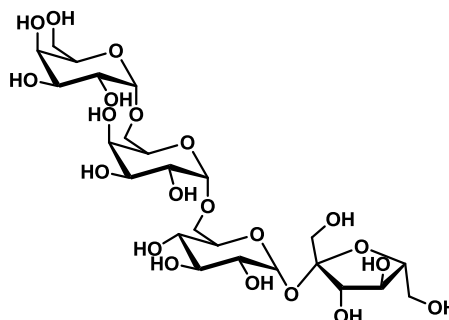
The importance of the separation and identification of saccharides has already been discussed. Existing SLM techniques have issues and so a boronic acid FCM system is a possible solution. When designing a FCM, a common approach is to take an existing membrane system, preferably one already showing partial activity in the desired area, and attach a fixed carrier to it. Not only is this potentially easier than creating a membrane system from scratch, it reduces the variables of the system to just the type and concentration of the carrier.

#### 2.3.1 Previous Work

The Perera group have previously investigated the use of novel fine pore hollow fibre membranes with regards to drug delivery,<sup>50</sup> tissue scaffolding<sup>51-53</sup> and gas separation.<sup>54,55</sup> More specifically, they have investigated making polymeric, zeolite and ceramic hollow fibre systems specifically for oligosaccharide separation and concentration from bulk solutions.<sup>56</sup>

A series of different fibres were synthesised aimed at having a molecular weight cut-off of less than 10 kDa, suitable for allowing the passage of oligosaccharide sized particles, but

rejecting anything larger. Fibre pore size and flux were tested both with dextrans (known size and weight polysaccharides) and the oligosaccharide stachyose **2.19**, with positive results.



**2.19**

Other work has been aimed at smaller saccharides. However, the separation of the near isomeric monosaccharides by hollow fibres, and thus size, was unsurprisingly not possible, no matter how small a pore size was produced. This inability to be selective for same sized molecules is exactly where adding fixed carriers could afford selectivity. Therefore, adding boronic acids to these existing hollow fibre membranes would potentially improve separation or grant a selectivity that was previously lacking.

### 2.3.2 Types of Fibre

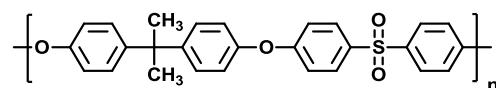
The previous study investigated ceramic, zeolite and polymeric hollow fibres, all of which have different properties and thus different suitabilities for the required task.

Ceramic hollow fibre membranes are formed out of inorganic materials such as alumina ( $\text{Al}_2\text{O}_3$ ), silica ( $\text{SiO}_2$ ) or titania ( $\text{TiO}_2$ ). They give membranes with extremely high chemical and thermal stability as well as high permeability,<sup>57</sup> but are difficult to functionalise. Functionalisation typically occurs by impregnating a group such as a metal salt within the membrane. Membrane reactors with catalytic palladium,<sup>58,59</sup> platinum,<sup>60</sup> ruthenium,<sup>61</sup> rhodium<sup>62</sup> and nickel<sup>63,64</sup> have all been produced. Unfortunately, this process is better suited to inorganic compounds, with organic additives limited to surface dip-



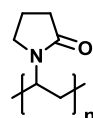
coating. As such, the ceramic hollow fibres used are probably unsuitable to adapt as boronic acid FCMs.

Polymeric hollow fibre membranes are the most common type of hollow fibre. Most of the previous examples of hollow fibre systems within the group are polymeric, and have used Udel polysulfone (PSF) **2.20**.



**2.20**

In comparison to inorganic membranes, they are much more susceptible to thermal and chemical degradation, but compensate by being easier to synthesise and work with (inorganic membranes tend to be brittle in nature). In order to improve the properties, a series of non-functional additives were investigated. PSF is a very hydrophobic polymer so the addition of the hydrophilic polymer polyvinylpyrrolidone (PVP) **2.21** increases water flux through the membrane.<sup>65,66</sup>



**2.21**

Alternatively, when silica is added to the polymer mix, macrovoids form around the particles, increasing the total free volume within the polymer and therefore increasing the rate of diffusion and solubility of the solute.<sup>67</sup> Additionally, pre or post treatment of the hollow fibres with sodium hypochlorite (NaOCl) increased pore size of the fibres (and thus flux) by both cleavage of polymer chains and the elimination of PVP from the polymer matrix.<sup>68</sup> In terms of functionalisation of the membrane, the PSF core is relatively reactive towards organic chemistry, compared to the ceramic fibres, so addition of a boronic acid unit is feasible.

The zeolite fibres, at least in the case studied, are effectively polymeric membranes with a zeolite additive. 4 Å zeolite particles added to the polymer blend simultaneously act like the silica particles in creating voids, whilst being an additional porous media. This creates a membrane akin to inorganic membranes without the fragile and brittle nature normally associated with them.<sup>69</sup>

Out of the three fibres investigated, polymeric or zeolite fibres would be most suited to further experimentation towards creating a boronic acid FCM. As mentioned above, the difficulty and limitations in functionalising a ceramic membrane with an organic group makes them unsuitable for use as the FCM. The difference between the polymeric and zeolite membranes studied is effectively an additive, so the need for zeolites can be decided later on whilst optimising the synthesised membranes. Given the extensive work previously carried out using Udel polysulfone, this would be a convenient starting point for functionalisation.

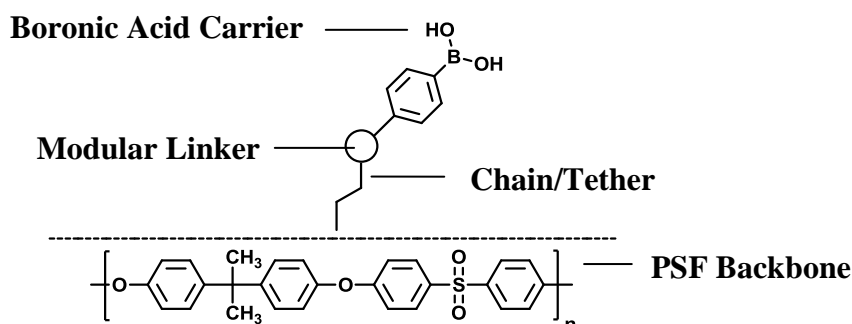
### 2.3.3 Boronic Acid FCM Hollow Fibre Implementation

Having established that Udel polysulfone hollow fibres are a good starting point for saccharide separation, the different routes to attach boronic acid carriers onto the hollow fibers need to be evaluated. The following requirements are highly desirable:

- **Covalently Anchored:** Increased membrane stability is a major reason for making a FCM, so it is prudent that the carrier is bound to the membrane as strong and stably as possible. Binding the carrier covalently means that the membrane will be resistant to mechanical degradation.
- **High Carrier Concentration:** The concentration of the boronic acid carrier will need to be high within the membrane as the degree of separation of the target analyte will be proportional to boronic acid content, or to potentially overcome a percolation threshold.

- **Modular Functionalisation:** As distinct boronic acid units can convey different selectivity onto target analytes, it is preferable that membrane modification is modular, to allow easy adaptation of the membrane to different targets.
- **Tethered Carrier:** It's preferable that the carrier is set away from the membrane wall to allow sufficient room for the saccharides to achieve the desired orientation with the boronic acid. Additionally this may aid the separation by facilitating fixed-site jumping by the limited diffusion of the chained carriers.

In summary, the aim is to make a membrane with a high density of boronic acid units covalently bound to the polysulfone making up the membrane. Preferably the boronic acids are linked by a tether or chain in such a way that a series of modular changes can be made, as represented in **Figure 2.8**.



**Figure 2.8:** Diagram of ideal membrane composition.

There are three routes which can be taken to achieve the desired system; homogeneous modification of polysulfone pre-membrane synthesis, heterogeneous modification of the hollow fibre post-membrane synthesis and functional monomer polymerisation.

### **2.3.3.1 Homogeneous Modification**

Polysulfone is chemically functionalised using standard solution-based chemistry. Once modified, the polysulfone is spun into hollow fibres to give the fixed carrier membrane. The method allows close control over the functionalisation and should give a high yield and even distribution of boronic acid. However, the change in composition of the polymer may negatively affect the spinning process and thus potentially require further optimisation to achieve the desired membrane.

### **2.3.3.2 Heterogeneous Modification**

Solid hollow fibre membranes are functionalised heterogeneously to give the finished membrane. As the functionalisation is post-spinning, the basic membrane properties should be unaffected by the process. The functionalisation itself however, will be more difficult. Yields will potentially be lower, modification may only occur at the surface of the polymer and characterisation of the reaction would be a destructive process (dissolution of part of the membrane).

### **2.3.3.3 Functional Monomer Polymerisation**

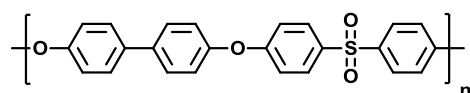
Rather than functionalising polysulfone directly, a polysulfone monomeric precursor is functionalised to give a modified monomer. This new monomer is then polymerised to give functionalised polysulfone, which is then spun into the finished membrane.

Chemistry on polymers is often difficult and has a range of possible problems including limited solubility and the potential for cross-linking side reactions, limitations generally absent from monomeric chemistry, thus monomeric functionalisation may prove a superior route. It does however, require the extra step to polymerise the monomers and functionalised polysulfone will still have the potential spinning problems as the homogeneous modification route. Alternatively, suitable functionalised monomers may already exist allowing simpler chemistry and fewer steps to be used to achieve the desired functionality.

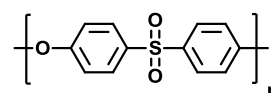
All three routes are viable and utilise subtly different chemical processes. The most important step, which makes up the bulk of research undertaken, is to complete the initial functionalisation, either through addition of functionality to the polymer, or polymerisation of the functionalised monomer. Once functionalised, subsequent modification is easier.

## 2.4 Polysulfone

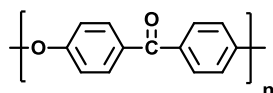
Udel Polysulfone (henceforth, referred to as polysulfone, or PSF) is a member of a family of polyarylene ethers. These include radel polysulfone **2.22**, polyethersulfone (PES) **2.23**, polyetherketone (PEK) **2.24**, polyetheretherketone (PEEK) **2.25** and polyetherketoneetherketoneketone (PEKEKK) **2.26**.<sup>70</sup>



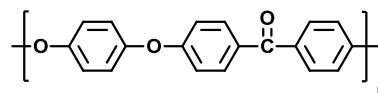
**2.22**



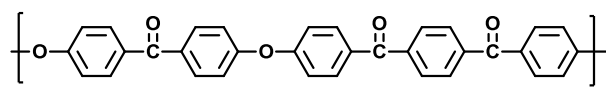
**2.23**



**2.24**



**2.25**



**2.26**

### 2.4.1 Properties

PSF is a high-performance engineering thermoplastic with superb thermal, mechanical, biological, hydrolytic and oxidative stability. It is resistant to extreme pH's and most

solvents, maintaining these properties over a range of -100 to 150 °C. It has low creep (deformation under stress), is dielectric (electrical insulator) and self-extinguishing.<sup>71-74</sup> The thermal and chemical stability stems from the highly resonance stabilised nature of the polymer. The inflexible sulfonyl units give mechanical strength and rigidity to the polymer chain, whilst the ether linkages, with their low barrier to rotation, give toughness and impact resistance by providing a route for energy dispersion.<sup>70,75</sup>

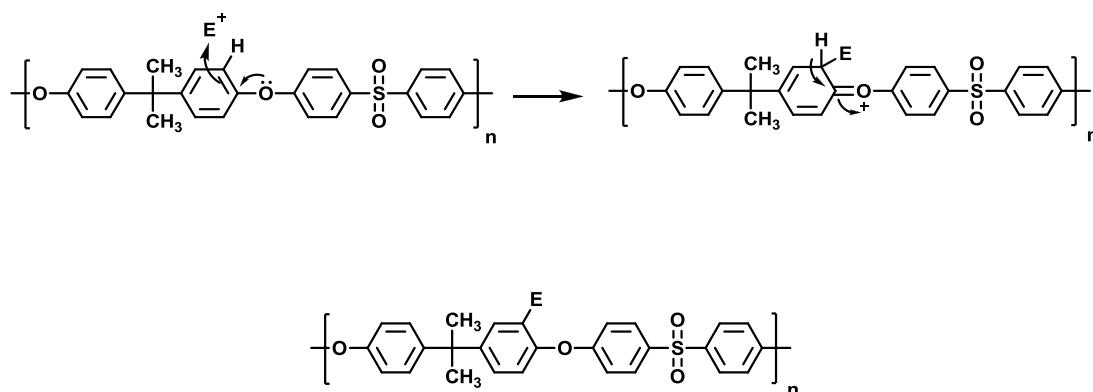
PSF is highly suited for membrane and hollow fibre synthesis, with excellent film-forming properties.<sup>76</sup> The high thermal stability allows melt spinning temperatures of up to 400 °C<sup>77</sup> and its wide soluble region in the phase diagram means that the porosity of spun membranes can be easily controlled by varying the composition of the casting solution (the ratio of PSF to solvent, additives etc.).<sup>78</sup> Additionally, its robustness lends itself to applications where the membrane is required to be sterilised, such as medical dialysis membranes; PSF is one of the few biomaterials able to withstand the common sterilisation techniques such as steam, ethylene oxide or gamma radiation.<sup>79</sup>

### 2.4.2 Reactivity

Although PSF's chemical stability is a desirable property for a membrane to possess, it also means that chemical functionalisation is difficult. As discussed in section 2.3.3, there are three routes towards the desired polymer: homogeneous modification, heterogeneous modification and functional monomer polymerisation. Whilst functional monomer polymerisation avoids the issue by functionalising relatively reactive monomers, homogeneous and heterogeneous modification routes both require the ability to directly functionalise the generally unreactive PSF. There are however, three ways in which this can be achieved: electrophilic aromatic substitution, lithiation and terminal group functionalisation.

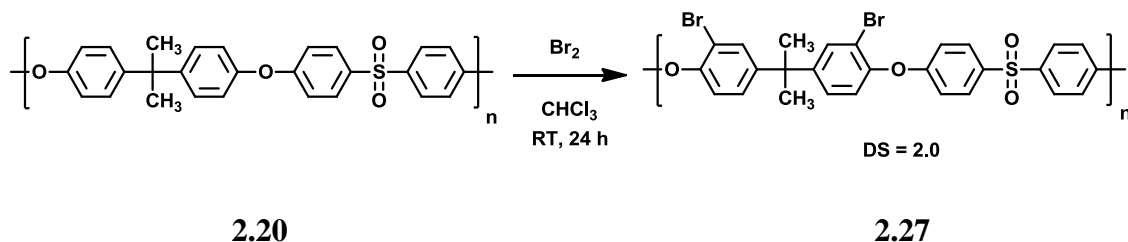
#### 2.4.2.1 Electrophilic Aromatic Substitution

Electrophilic aromatic substitution can occur *ortho* to the ether linkages on the electron rich bisphenol A unit. This adds the electrophile directly to the polymer backbone as shown in **Scheme 2.1**.



Scheme 2.1

These reactions generally require forcing conditions, such as the high temperatures and strong acids needed for nitration<sup>80</sup> or sulfonation.<sup>81</sup> Alternatively, metal catalysed Friedel-Crafts type reactions can append a variety of groups under milder conditions such as Blanc chloromethylation.<sup>82</sup> Perhaps the best example of electrophilic aromatic substitution of PSF is the aromatic bromination shown in **Scheme 2.2**.<sup>83</sup>

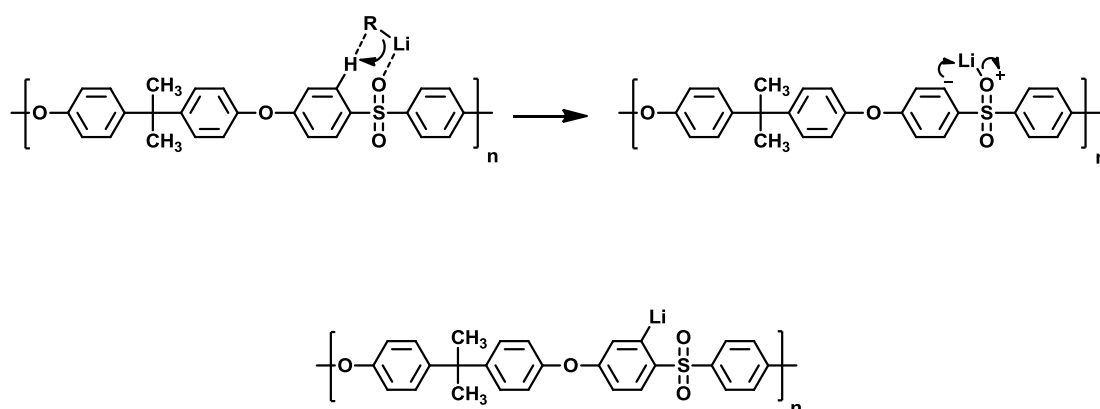


Scheme 2.2

This is an ideal reaction as it rapidly and cleanly gives a functionalised polymer with no polymer degradation or side products, consistently affording a degree of substitution (DS) of 2.0. The brominated PSF (PSFBr) **2.27** gives a polymer with a fixed amount of reactive sites from which further functionalisation can occur. Standard aryl bromide chemistry, such as Suzuki cross-coupling or lithium halogen exchange will react solely or preferentially at the brominated sites, thus the selectivity from the original bromination is continued through to the subsequent functionalisations.

### 2.4.2.2 Lithiation

Lithiation, unlike electrophilic aromatic substitution, happens *ortho* to the sulfone moiety. This regioselectivity stems from the oxygen of the sulfone both directing the deprotonation and stabilising the lithium cation during the reaction. **Scheme 2.3** gives a postulated mechanism for the lithiation of PSF.<sup>84</sup>

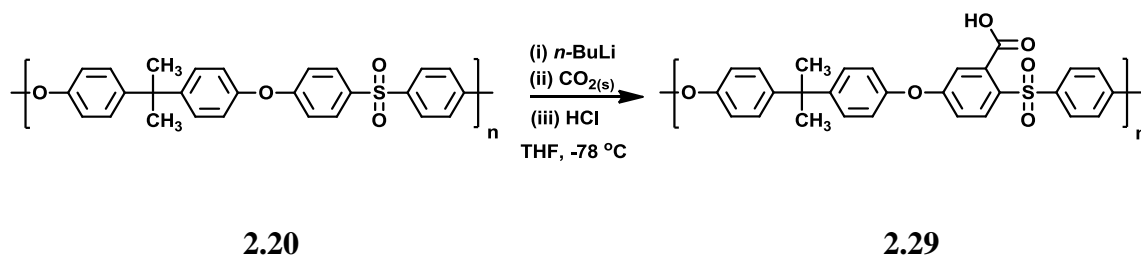


**2.28**

**Scheme 2.3**

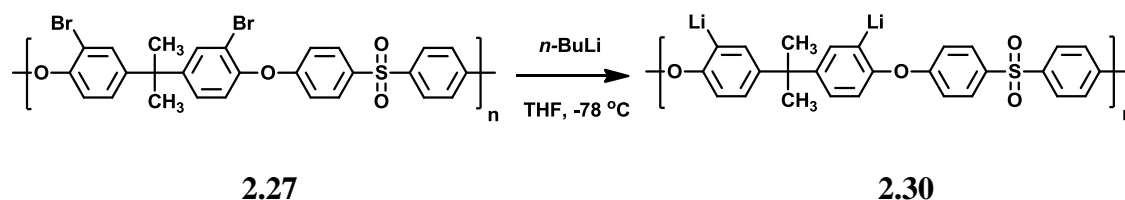
The lithiated PSF (PSFLi) **2.28** is highly reactive and will undergo electrophilic substitution at the lithiated position. Compared to the *ortho*-ether electrophilic substitution, the lithium mediated reaction will react with a much wider range of electrophiles under mild conditions. The reaction with dry ice (CO<sub>2(s)</sub>) gives the carboxylated polymer **2.29** (**Scheme 2.4**) and showcases this increased reactivity.<sup>85</sup> The transformation cannot easily occur *ortho*-ether. Reaction yields can be controlled easily by adjusting the amount of lithiating reagent as the limiting reagent, and adding excess electrophile to quench every lithium site.





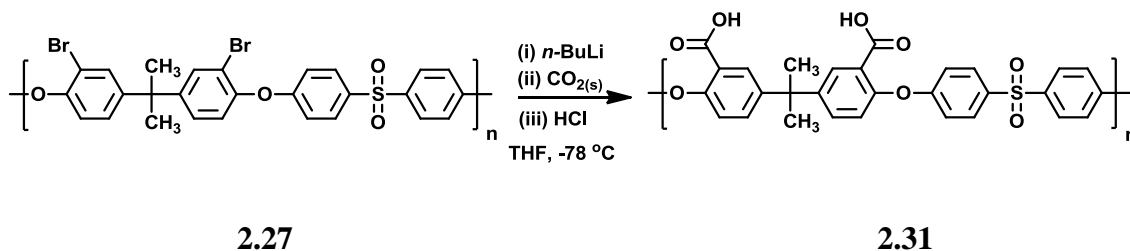
Scheme 2.4

When PSFBr **2.27** is reacted with a lithiating reagent, halogen-lithium exchange *ortho*-ether occurs preferentially to the usual *ortho*-sulfone lithiation to afford *ortho*-ether lithiated PSF **2.30** (Scheme 2.5).<sup>83</sup>



Scheme 2.5

This process gives us access to *ortho*-ether functionalised PSFs which are inaccessible by conventional electrophilic aromatic substitution methods. For example, the aforementioned carboxylation can now produce *ortho*-ether carboxylated PSF **2.31** as shown in Scheme 2.6<sup>83</sup>

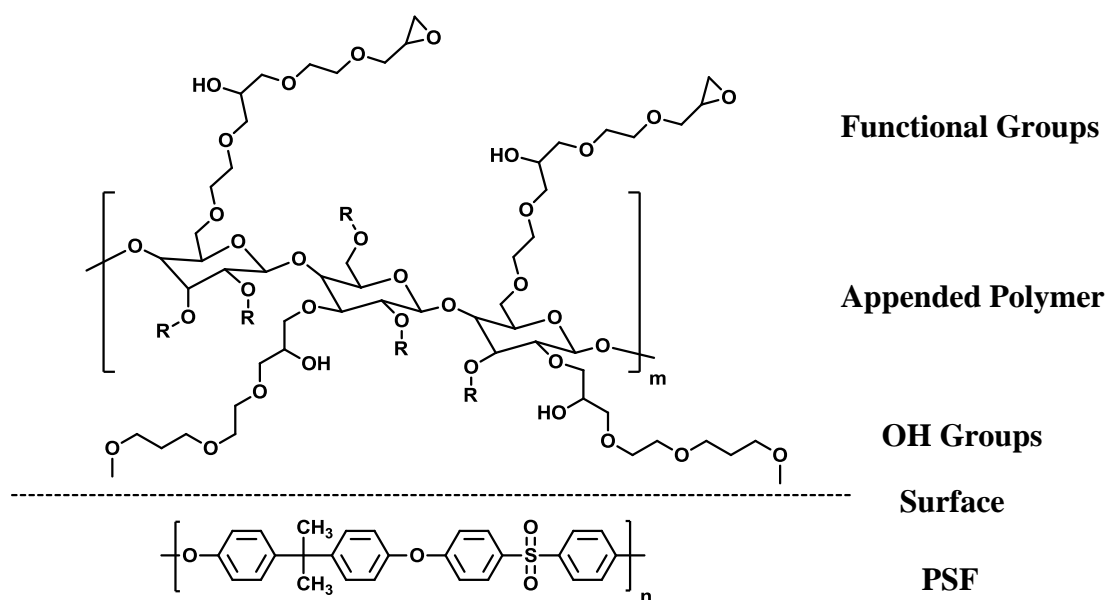


Scheme 2.6

### 2.4.2.3 Terminal Group Functionalisation

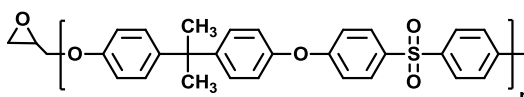
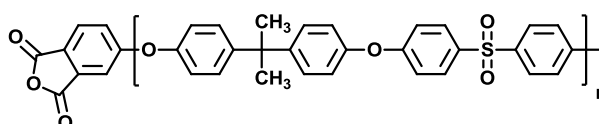
The previous two methods described directly functionalise the polymer backbone whereas terminal group functionalisation functionalises the terminal hydroxyl groups on the polymer chain. Udel PSF P-1700 NT-11 has a molecular weight of around 100,000 and the molar mass of the monomer is roughly  $445 \text{ g mol}^{-1}$ , therefore there are approximately 100 monomer units per terminal hydroxyl group. Although the hydroxyl groups are very easy to functionalise, the large size of the PSF chain means that the relative concentration of the hydroxyl groups is very low so limited functionalisations are possible.

One solution to this issue uses the hydroxyl groups to tether a second functional polymer to the PSF, effectively adding multiple functional groups to one end group. This is often a route to simple heterogeneous surface modification of hollow fibres, as shown by the work of Beutel *et al.*<sup>86</sup> Step-wise modifications provided PSF and PES hollow fibres with a surface layer of hydroxyethyl cellulose polymer appended with reactive epoxide terminated chains (**Figure 2.9**). The terminal epoxides can be further modified with a range of amines to give surface groups capable of chelating various metals.



**Figure 2.9:** Terminal hydroxyl surface modification of PSF.

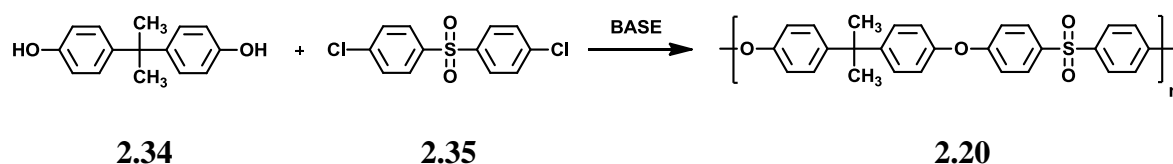
The terminal hydroxyl groups can also be functionalised to facilitate easier formation of block copolymers, by attaching a more reactive linking moiety. Inoue *et al.*<sup>87</sup> functionalised PSF terminal groups with reactive epoxide and phthalic anhydride to form **2.32** and **2.33** respectively which when melt-mixed with polyamide formed a block copolymer *in situ*.

**2.32****2.33**

Terminal group functionalisation is generally unsuitable for the needs of this research. The low number of hydroxyl groups means direct functionalisation will not yield a high enough carrier concentration and tethering a secondary polymer will leave the carriers too far removed from the porous membrane wall to effectively exert any selectivity. Contrastingly, electrophilic aromatic substitution and lithiation are both suitable methods for achieving the desired level of functionalisation

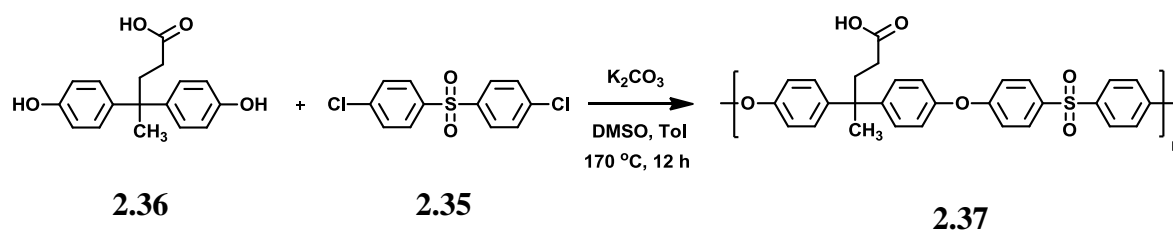
#### 2.4.2.4 Functional Monomer Polymerisation

As mentioned in section 2.3.3.3, a functionalised PSF can be produced by using an already functionalised monomer unit when polymerising, avoiding potentially difficult chemistry. The general synthesis of PSF from monomers involves the reaction of bisphenol A **2.34** with 4,4'-dichlorodiphenyl sulfone **2.35** and an alkali base to give the desired polymer, as shown in Scheme 2.7.<sup>70</sup>



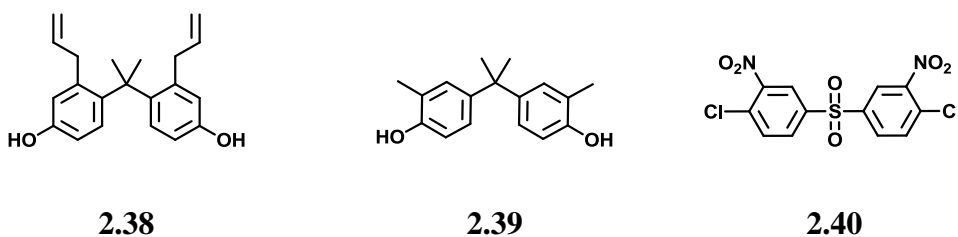
Scheme 2.7

Modifying the monomers or replacing either of them with a suitably functionalised monomer will give functionalised PSF. The functional group on the monomer would need to be suitable for our purposes and must not interfere with the polymerisation. For example, substituting bisphenol A for the commercially available analogue 4,4-bis(4-hydroxyphenyl)valeric acid **2.36** in the polymerisation with 4,4'-dichlorodiphenyl sulfone **2.35** yields carboxylated PSF **2.37**<sup>88</sup> (Scheme 2.8).



Scheme 2.8

There is a large range of commercially available monomers with the potential to give a variety of functionalised PSFs, including 2,2'-diallylbisphenol A **2.38**, 2,2-Bis(4-hydroxy-3-methylphenyl)propane **2.39** and 4-chloro-3-nitrophenyl sulfone **2.40**.



### 2.4.3 Challenges of Polymer Chemistry

There is a range of potential ways to functionalise PSF, however, the nature of polymers and polymer chemistry presents further difficulties that are not present within unimolecular chemistry and must be overcome to achieve the desired results.

#### 2.4.3.1 Solubility

PSF is an extremely hydrophobic, long chain polymer and so it is not surprising that it has limited solubility in common laboratory solvents. It dissolves only in polar aprotic solvents like tetrahydrofuran (THF) or asymmetric halogenoalkanes such as chloroform and dichloromethane (DCM), and requires a relatively large amount of solvent. *N*-methylpyrrolidone (NMP) gives greater solubility, but at the expense of having an extremely high boiling point of 202 °C.

The limited solubility in itself is not a large concern outside of limiting certain reaction conditions, or the availability of solvents for analytical techniques such as NMR. The difficulty is when PSF is functionalised, with both the type of functional group and the degree of functionalisation greatly affecting the solubility.

Addition of hydrophobic groups generally has little effect. However, addition of hydrophilic groups such as boronic acids, have a much bigger influence; the hydrophobic nature of the polymer backbone competes with the hydrophilic nature of the added groups. When only functionalised to a small degree, the solubilising properties largely come from PSF and thus it will dissolve in the usual organic solvents. When highly functionalised, the functional groups will have a greater influence on the solubility, simultaneously reducing the solubility in organic solvents and increasing the solubility in aqueous solvents.

Unfortunately, when partially functionalised, the hydrophobic and hydrophilic natures compete and cause the polymer to have lower solubility in both aqueous and organic solvents.

Guiver *et al.*<sup>85</sup> investigated the solubility of carboxylated PSF **2.29** in relation to varying degrees of substitution. There are two reaction sites per monomer unit so each monomer can be modified up to two times. PSF carboxylated up to 30% retained solubility in the

normal solvents such as chloroform and DCM. In comparison, PSF carboxylated between 140-190% was insoluble in both chloroform and DCM, but had become soluble in acetone instead. However, PSF carboxylated between 30-140% showed poor solubility with most solvents, being insoluble in chloroform, DCM and acetone.

This relationship between solubility and substitution can also severely reduce the level of substitution achieved. As a reaction progresses and the level of substitution increases, it is possible that the PSF will become insoluble before the reaction reaches completion. Within unimolecular chemistry, precipitation of the product is not a concern as unreacted starting material will remain in solution and continue to react. In fact, precipitation of a product will often push a reaction towards completion. When a polymer starts to lose solubility however, both reacted and unreacted sites will be pulled out of solution limiting the reaction. The reaction yield is effectively limited by the solubility of both the starting polymer and the product. This often necessitates the use of NMP or dimethylsulfoxide (DMSO) as solvents as they can solvate the widest range of PSF.

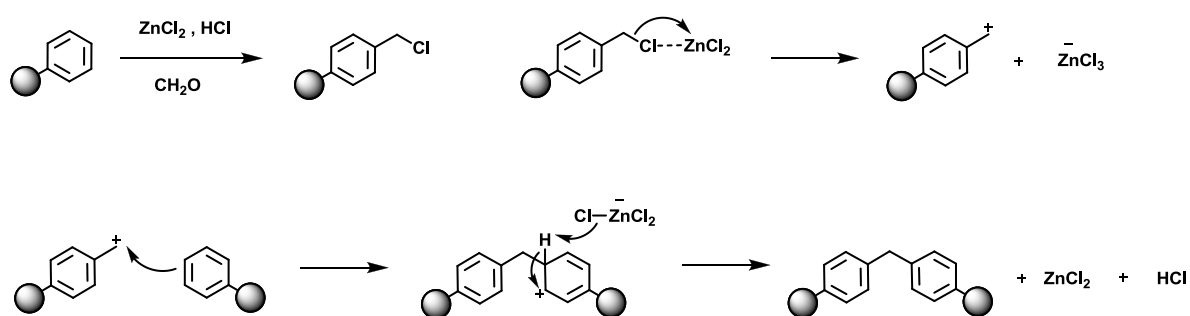
### 2.4.3.2 Side Reactions and Purification

Within unimolecular chemistry, when reactions fail to go to completion or produce unwanted side reactions, impurities can be separated from the desired product using standard purification techniques. Generally the only effect of this is to lower the overall yield of the reaction; the isolated product is pure. With polymers however, any side products produced will invariably be attached to the same polymer chain as the desired product. Unsurprisingly, it is impossible to separate the side products from the desired product as they are joined together. This is a major concern as it means that side reactions, rather than lowering the overall yield of the reaction, instead contaminate the product.

For example, assuming a hypothetical unimolecular reaction produces 90% product and 10% side product, the overall yield of the reaction will be 90% pure product. Taking the same hypothetical reaction and applying it to polymer chemistry will produce 100% of a polymer with a 9:1 ratio of desired and undesired functionality.

This means that functionalisation on polymers either has to be a very clean process that produces minimal side products, or the side products produced do not interfere with the function of the polymer or its further chemical synthesis.

Cross-linking is a specific side reaction whereupon a molecule of product reacts with a molecule of starting material linking them together. It is a significant difficulty with polymer chemistry. When cross-linking occurs in unimolecular chemistry it results in production of a side product and a loss of overall yield like any other side reaction. In polymer chemistry however, even small amounts of cross-linking side reactions become a problem. It can create multiple polymer chains linked together or folding chains when two sites on the same chain react. This is more destructive than regular side reactions as the cross-linked polymer chains can easily lose all solubility, even at low levels of cross-linking, making them entirely unsuitable for further use. An example where this is prevalent is in Blanc chloromethylation of aryles, where the resultant chloromethyl group is active towards Friedel-Crafts alkylation type reactions and can therefore cross link with the unreacted aryl units.<sup>89</sup> **Scheme 2.9** shows a proposed mechanism for the cross-linking reaction.<sup>90</sup>



**Scheme 2.9**

Typically in unimolecular chemistry, the cross-linking side reaction can be suppressed by adjusting the reactants and reaction conditions, with the concentration of the reactants in solution being the biggest influence. Unfortunately, regardless of the concentration of a

polymer in solution, there will always be a high “effective concentration” of reactive sites. In a regular system, the effect of reducing the concentration of a reactant within a solution is to increase the distance between reactants and thus reduce the chance that they react. With a polymer, whilst reducing its concentration in solution will increase the distance between reactive sites of distinct polymer chains, i.e. intermolecularly, it will not reduce the distance between active sites within the same chain, i.e. intramolecularly. This means that reduction in concentration of a polymer solution will only reduce the reactivity to a point, with the polymer behaving as if it was higher in concentration, thus having a high effective concentration. As such, avoiding cross-linking is not a simple case of increasing the amount of solvent in the reaction, very specific reaction conditions are required, as shown by Avram *et al.*<sup>91</sup> for the chloromethylation of PSF.

Another possible issue regarding effective concentration and the proximity of reactive sites is the potential for added functional groups to interfere with the functionalisation of their neighboring reactive sites, either chemically or sterically. The effect of this would be to limit the overall yield of the reaction by lowering the reactivity of the polymer past a degree of substitution.

#### **2.4.3.3 Analysis**

Due to the nature of polymers, the standard analytical techniques used to follow reactions and identify products are not entirely applicable. Mass spectrometry (MS), nuclear magnetic resonance spectroscopy (NMR) and X-Ray crystallography (XRD) are the cornerstone of synthetic chemistry, but all have varying degrees of suitability for polymer chemistry.

Single crystal x-ray diffraction is one of the most powerful techniques available. It is able to determine the exact composition and structure of a compound, but it requires the analysed material to be crystalline. Polymers such as PSF are unable to form single crystals, and so x-ray analysis is restricted to more limited x-ray techniques. For example, x-ray photoelectron spectroscopy (XPS) can be used to investigate the surface of PSF membranes<sup>92</sup> and wide-angle x-ray scattering (WAXS) can measure the *d*-spacing<sup>93</sup> (how the polymer chains are packed together), but they are unsuitable for quantitative analysis of functionalisation.



MS functions directly to measure the molar mass of a compound, as well as elucidate structure through the analysis of fragments. Due to the large size and polydispersity of polymers such as PSF, obtaining a total mass is often difficult,<sup>94</sup> however, smaller oligomeric fragments can be investigated to give an idea of the structure.<sup>95</sup> Matrix-assisted laser desorption/ionisation – time of flight MS (MALDI-TOF) has previously been used to study impurities within PSF<sup>94</sup> and investigate potential decomposition routes and products.<sup>96</sup> Unfortunately, our attempts at characterising PSF by electrospray ionisation – time of flight MS (ESI-TOF) and atmospheric-pressure chemical ionisation – time of flight MS (APCI-TOF) failed to give any meaningful results. As such, the MS facilities at the University of Bath could not be used to identify functionalised PSF we synthesised.

Unlike MS and XRD, PSF and its derivatives are readily identified by simple NMR techniques, producing clear spectra and allowing quantitative measuring of functionalisation. The major difficulty comes with PSF's solubility which limits the available deuterated NMR solvents that can be used. Whilst  $\text{CDCl}_3$ ,  $\text{DCM-d}_2$  and  $\text{DMSO-d}_6$  are commonly available and will solvate a wide range of functionalised PSF, the prohibitive cost of  $\text{THF-d}_8$  and  $\text{NMP-d}_9$  means they are unable to be used as general solvents, meaning some functionalised PSFs cannot be identified by NMR.

Overall, this means that the bulk of the analysis is limited to NMR, supported by the secondary analytical techniques of infrared spectroscopy (FT-IR) for confirming non-NMR active functional groups, and gel-permeation chromatography (GPC) for the determination of molecular weight and other polymeric properties.

#### **2.4.3.4 Reaction Scale**

The PSF hollow fibres which form the basis of our research are made by the dry-wet spinning method, described in section **1.6.1**. Specifically, the spinning apparatus requires a minimum amount of polymer solution in order to make useable fibres, with the minimum polymer solution typically consisting of 20-25 g of PSF mixed with 75-80 g of solvent, plus any additives such as silica or PVP.<sup>56</sup> In theory, PSF from failed membranes could be recycled, but the common post treatments such as  $\text{NaClO}$  can be destructive to the polymer

meaning fresh PSF needs to be synthesised for each spinning run. In terms of synthetic chemistry, this equates to a large amount of material, ideally several hundred grams and thus will require large scale reactions in order to make the process efficient.

### **2.5 Conclusion**

This chapter has discussed how there is a need for systems capable of detecting and/or separating saccharides for important tasks such as diabetes monitoring, disease biomarker detection and commercial sugar separation. Currently there are a range of methods capable of these tasks, but they have issues with selectivity and stability which could be improved upon. It is theorised that a boronic acid fixed carrier hollow fibre membrane could give the desired selectivity and separation effects with excellent stability.

From previous studies, PSF hollow fibres were identified as being suitable, and therefore the functionalisation and synthesis of PSF has been the centre of this research. Three general routes have been identified to achieve the desired polymers: electrophilic aromatic substitution, lithiation and functional monomer polymerisation. Clean, high yielding chemistry suitable for scale up is required to create functionalised PSF of the quality and quantity needed for the creation of effective membranes.

The following chapters discuss the routes undertaken to synthesise functionalised PSF.

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## Chapter 3 : Functionalisation of Polysulfone *via* Electrophilic Aromatic Substitution

### 3.1 Introduction

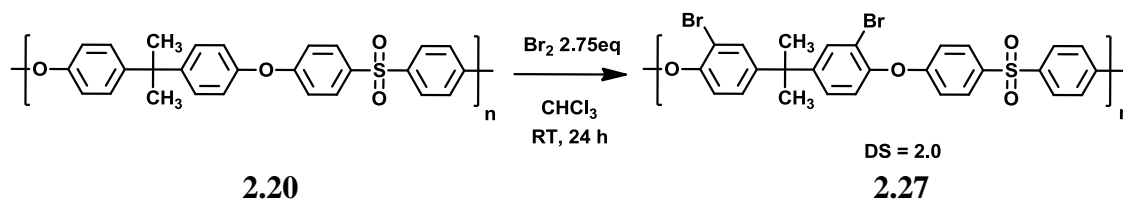
The following chapter discusses the routes and attempts undertaken to functionalise PSF initiated by electrophilic aromatic substitution methods.

### 3.2 Bromination

As mentioned in section **2.4.2.1**, bromination of PSF is an ideal reaction for our purposes. It is a quick and clean reaction, using ambient conditions, and reproducibly gives dibrominated PSF (DS = 2.0) with no chain degradation on a large scale. This is the ideal standard required to give the desired polymer, a standard with which subsequent electrophilic aromatic substitutions should adhere to. The key requirement is for a clean high yielding reaction which can be easily reproduced.

PSF was initially brominated by Ohmae *et al.*<sup>1</sup> by refluxing bromine in combination with an iron catalyst to produce perbrominated PSF. Unfortunately this produced discoloured and brittle polymer, owing to chain degradation caused by the high temperatures and large amounts of hydrobromic acid (HBr) given off by the reaction. Daly *et al.*<sup>2</sup> and Guiver *et al.*<sup>3</sup> concurrently discovered that these forcing conditions are not necessary to give a relatively highly brominated PSF.

Following their reported conditions dibrominated PSF **2.27** (DS = 2.0) was formed by adding a slight excess of bromine (2.75 equivalents, which equates to 1.375 equivalents per bromination) to PSF **2.20** dissolved in the minimum amount of chloroform and stirred at room temperature (**Scheme 3.1**).



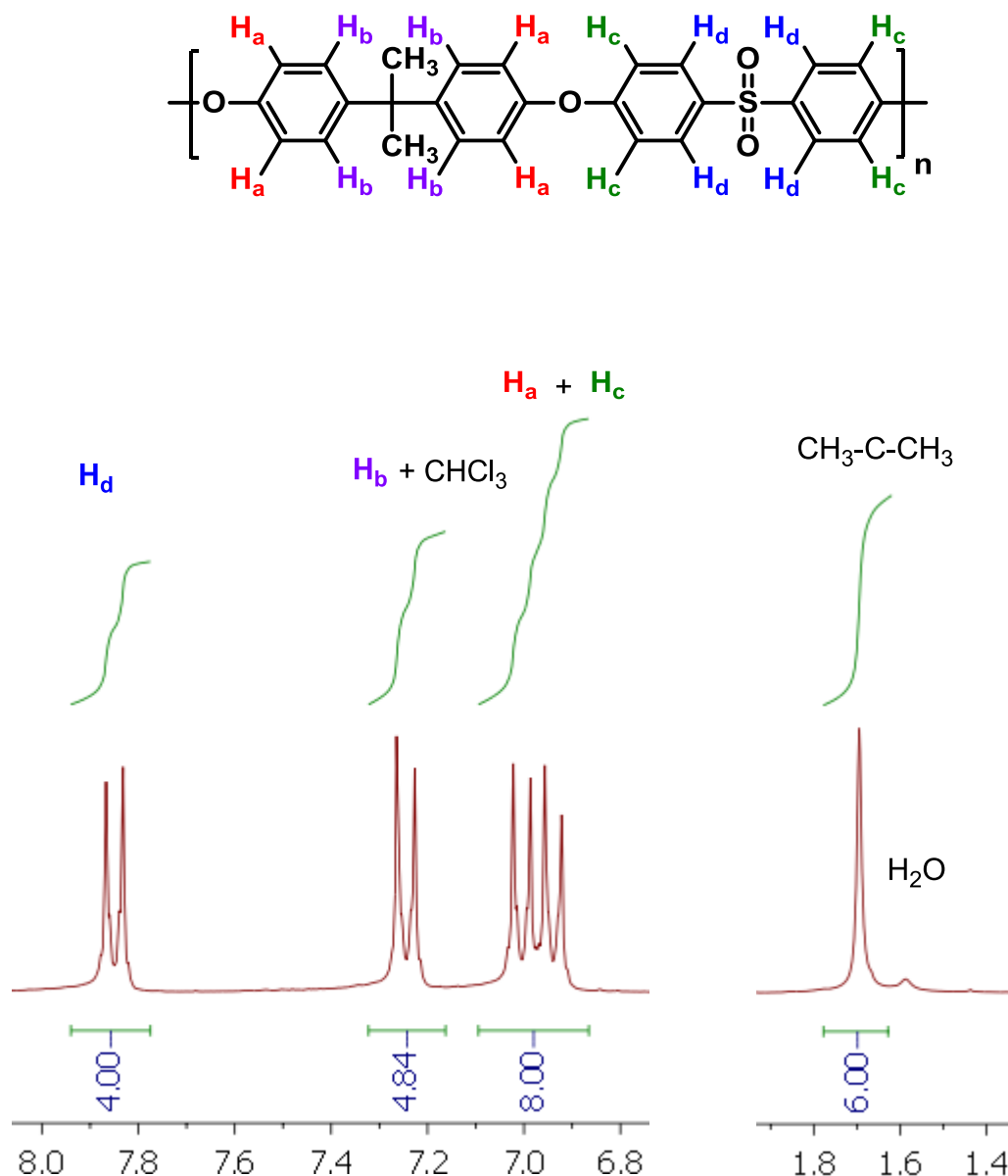
Scheme 3.1

The only by-products of the reaction are residual bromine and eliminated HBr, which can be leached out of the final polymer by stirring in methanol followed by thorough drying in a vacuum oven. Whilst this process is time consuming, taking 2-3 days to completely clean and dry the polymer, the PSF produced is 100% pure. Within our study, the reaction was successfully scaled up from the reported 11 g of PSF starting material to a 50 g reaction with no adverse effects. In fact, it is reported that the reaction has been scaled up to a 442 g scale with no detriment.<sup>3</sup> Interestingly, when the reaction was attempted at reflux, the DS decreased, indicating that the elevated temperatures coupled with the HBr generated was strong enough to interfere with the reaction.

Since the MS available to us were unsuitable for analysing the produced polymer, as discussed in section 2.4.3.3, only NMR was used to identify the product. The process of interpreting the <sup>1</sup>H NMR is slightly different from unimolecular chemistry as it requires comparison of the integrals of unchanged peaks with newly created ones; either the gem dimethyl group of the bisphenol A section or one of the aromatic protons on the section of the polymer which didn't react. This choice however, is also dependent on the solvent used for the NMR; in CDCl<sub>3</sub> the residual H<sub>2</sub>O peak at δ1.56 ppm often overlaps with the gem dimethyl peak and the residual CHCl<sub>3</sub> peak at δ7.26 ppm potentially interferes with the aromatic signal.

The <sup>1</sup>H NMR of unreacted PSF in CDCl<sub>3</sub> gives a simple spectrum with clear aromatic splitting (**Figure 3.1**). The CHCl<sub>3</sub> signal overlaps with the aromatic H<sub>b</sub> doublet making integration inaccurate. The other peaks however, are not obscured and integrate perfectly.

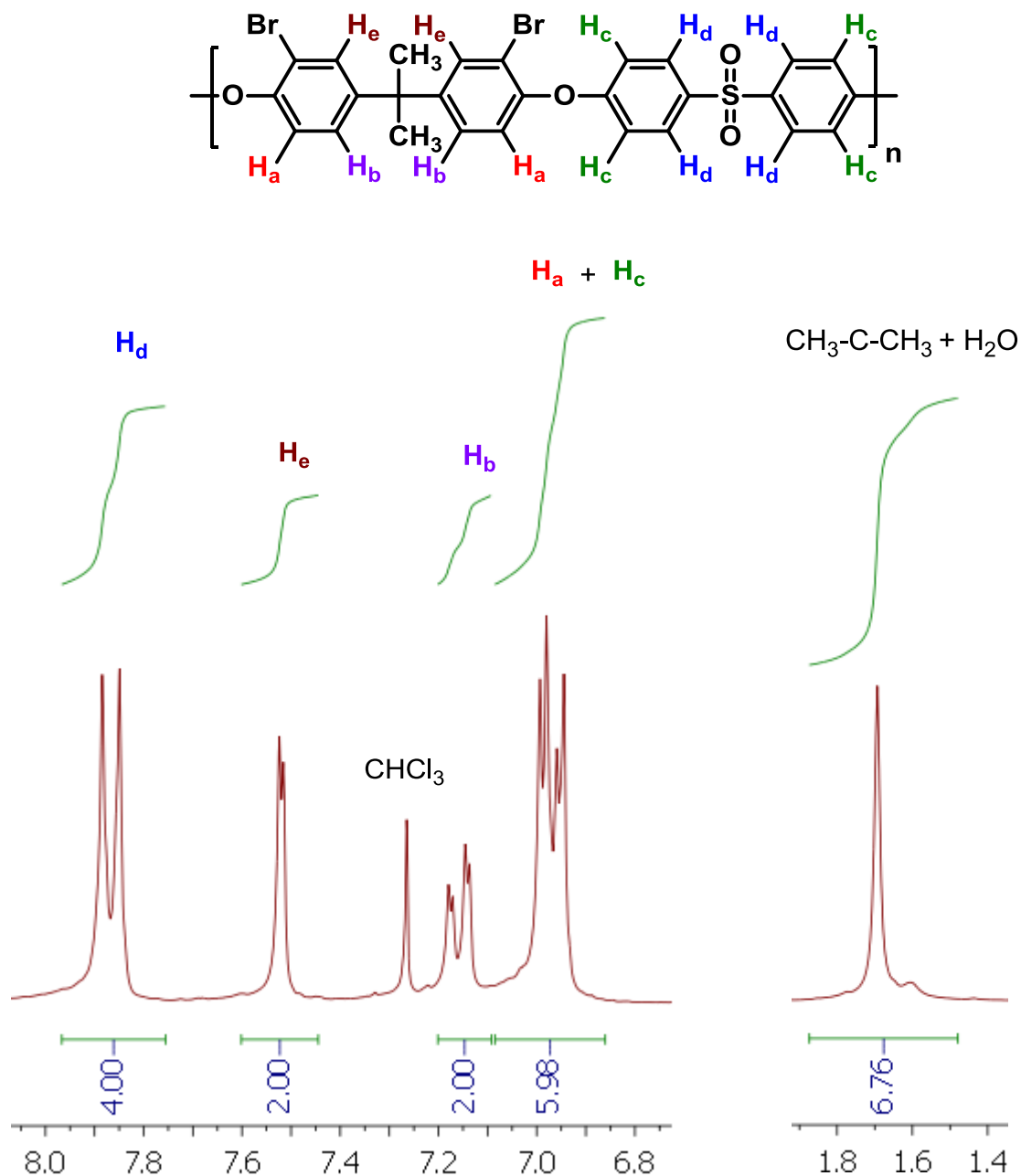
The two doublets of H<sub>a</sub> and H<sub>c</sub> are too close together to integrate separately, but can be integrated together.



**Figure 3.1:** 300 MHz  $^1\text{H}$  NMR of PSF in  $\text{CDCl}_3$ .

Upon dibromination two of the  $\text{H}_a$  protons are substituted by Br, reducing the integration by two (**Figure 3.2**). At the same time, influence from the new Br group creates a new environment, splitting the original  $\text{H}_b$  signal (7.24 ppm, d,  $J = 8.8$  Hz) and shifting the new  $\text{H}_b$  doublet of doublets upfield (7.15 ppm, dd,  $J = 8.5, 2.2$  Hz) and creating a new doublet  $\text{H}_e$  downfield (7.51 ppm, d,  $J = 2.2$  Hz). The  $\text{CHCl}_3$  peak is now no longer overlapping with any other peak.





**Figure 3.2:** 300 MHz  $^1\text{H}$  NMR of brominated PSF in  $\text{CDCl}_3$ .

As the  $\text{H}_d$  peak is unaffected by the reaction, it can be used as the internal standard to work out the reaction yield. Comparison of  $\text{H}_d$  with  $\text{H}_e$  shows a 2:1 ratio, indicating for every 2  $\text{H}_d$  protons, there is 1  $\text{H}_e$  proton. The amount of  $\text{H}_e$  protons is also equivalent to the amount of bromine present, and thus the degree of bromination. So, with 4  $\text{H}_d$  and 2  $\text{H}_e$  protons there are 2 Br, which indicates a degree of substitution of 2.0. This is the standard method we used for working out reaction yields in terms of degree of substitution (DS). Traditional

yields (i.e. weight of product/weight of starting material) are generally not relevant to this chemistry as material is rarely lost. The  $^1\text{H}$  NMR in this case is straightforward due to the symmetric degree of substitution. However, when the PSF is functionalised to anything other than  $\text{DS} = 1.0$  or  $2.0$  the  $^1\text{H}$  NMR becomes complicated, with effectively a mixture of starting material and product being present in the same polymer.

As well as being a model electrophilic aromatic substitution reaction, the brominated PSF is a useful reactive polymer, able to potentially undergo Suzuki or halogen-lithium exchange reactions, as discussed later.

### 3.3 Chloromethylation

#### 3.3.1 Introduction

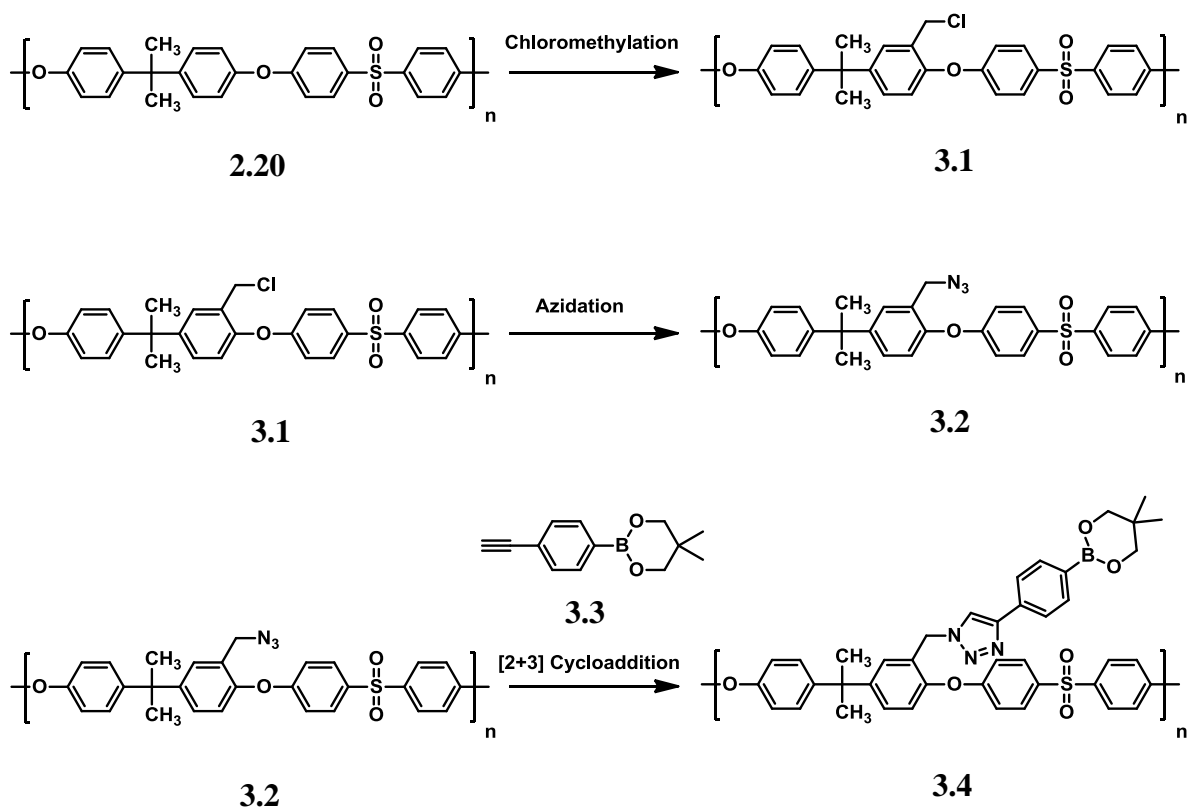
The next functionalisation of PSF investigated was metal catalysed chloromethylation. It was chosen due to the extensive literature precedence for the reaction and the ease at which subsequent functionalizations take place; chloromethyl groups are capable of undergoing a range of nucleophilic substitution type reactions.

First discovered by Blanc *et al.*<sup>4</sup> the transformation, at least in terms of polymer chemistry, is perhaps most well-known for the Nobel Prize winning work of Merrifield *et al.*<sup>5</sup> in the field of solid supported peptide synthesis. Merrifield resin consists of chloromethylated cross-linked polystyrene, where the chloromethyl group readily reacts with the carboxylic acid moiety of amino acids, binding them to the solid phase.

In order to create a polymer with the desired tether which could be modularly functionalised, the copper catalysed Huisgen [2+3] cycloaddition was an obvious choice. The reaction is the most prominent member of the family of so called “click reactions”, popularised by Sharpless *et al.*<sup>6</sup>, which proceeds in high yields whilst tolerating a wide range of conditions and competing functionality.

## 3.3.2 Design

A synthetic route to a desired polymer *via* chloromethylation is proposed in **Scheme 3.2**.



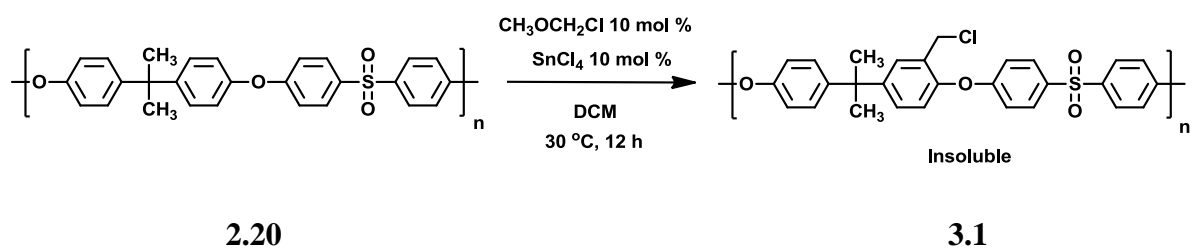
Scheme 3.2

After chloromethylation, the chloromethyl group can be converted into an azide *via* reaction with  $\text{NaN}_3$  under standard conditions<sup>7</sup> and subsequently “clicked” with an appropriate alkynyl aryl boronate. This methodology would ideally give a highly functional polymer which can effectively be modified with a range of alkynyl compounds.

Subsequently to our work Gaina *et al.*<sup>8</sup> has produced a series of “clicked” PSFs. They synthesised azidomethylated PSF **3.2**, in quantitative yields, by stirring chloromethylated PSF **3.1** with excess  $\text{NaN}_3$  in DMF for 10 hours at 65 °C. They then reacted **3.2** with a range of simple acetylene derivatives alongside TMEDA and  $\text{CuBr}$  to give the “click” products, again in quantitative yields.

### 3.3.3 Synthesis

The first attempted route at producing chloromethylated PSF was an adaptation of the work by Higuchi *et al.*<sup>10</sup> who used chloromethyl methylether (MOMCl) with SnCl<sub>4</sub> or ZnO as the catalyst to heterogeneously surface modify PSF hollow fibres (**Scheme 3.3**). Perhaps unsurprisingly, the conditions did not transition successfully to homogenous chemistry, with the reactions producing an extremely insoluble gel.

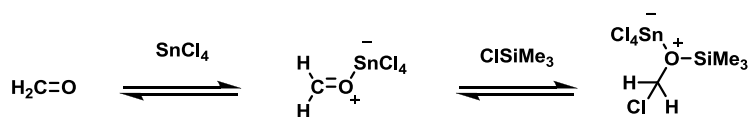


**Scheme 3.3**

Cross-linking, as discussed in section 2.4.3.2, is a serious problem for PSF functionalisation as the produced polymers lose solubility and functionality due to the methylene bridges. In the homogeneous reaction shown in **Scheme 3.3**, there was a complete loss of solubility, such that the produced PSF could not be analysed or used further. The problem is less significant for heterogeneous surface modification of PSF hollow fibres. The rigid nature of the fibres potentially lowers the rate of cross-linking and solubility is not a required property. However, the reported overall yields of the reaction were too low to be a useful route for us.

The chloromethylation of PSF has been extensively investigated by Avram *et al.*<sup>11-13</sup> They employed conditions developed by Itsuno *et al.*<sup>14</sup> for the chloromethylation of cross-linked polystyrene. The method uses a mixture of trimethylsilyl chloride (TMSCl) with trioxane or paraformaldehyde, alongside the usual SnCl<sub>4</sub> catalyst to generate the chloromethylating species *in situ* (**Scheme 3.4**). The major advantage of this method is that it greatly lowers the exposure time to potentially carcinogenic materials; MOMCl is a category 1A carcinogen. Specifically, SnCl<sub>4</sub> is added to a solution of PSF, TMSCl and

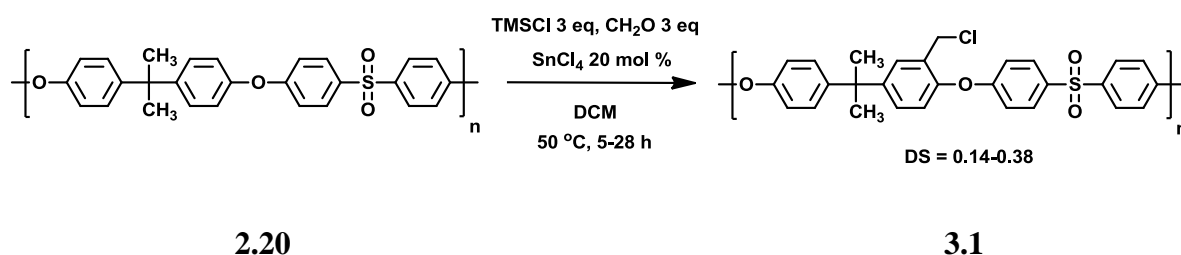
paraformaldehyde, such that the chloromethylating agent is only generated in the reaction mixture, with any excess being destroyed upon workup with methanol.



**Scheme 3.4**

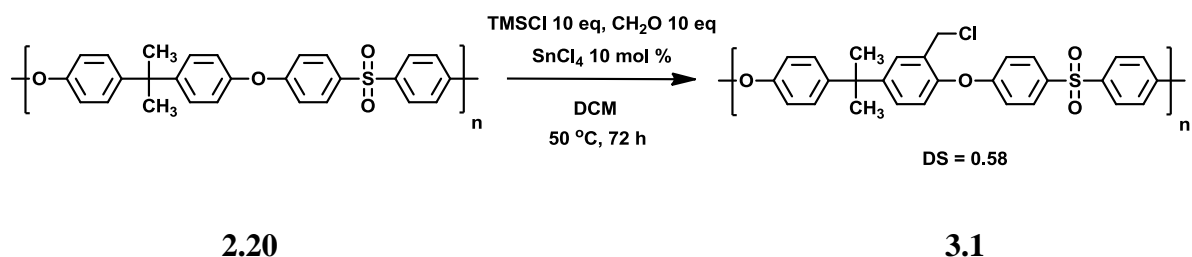
Stringent reaction conditions were required in order to give a high degree of substitution whilst keeping cross-linking to a minimum. A relationship was established between PSF concentration within the solution and the level of cross-linking occurring. It was reported that keeping the PSF concentration at around 2% generally prevented cross-linking. This is in stark contrast to the initial chloromethylation attempted in this study, where the minimum amount of solvent was used and cross-linking occurred, even with a low equivalent of MOMCl. It was also reported that an increased catalyst concentration also caused cross-linking, with 50 mol % or more of catalyst causing insoluble polymers and 10-20 mol % of catalyst being optimum. With these restrictions, the chloromethylating reagent and length of reaction time become responsible for the degree of substitution.

It was reported that a mixture of 3 equivalents of chloromethylating reagent (1:1 TMSCl and paraformaldehyde) mixed with 1 equivalent of PSF and 20 mol % of  $\text{SnCl}_4$  gave polymers chloromethylated with a DS up to 0.41, 0.63 and 0.80 after 5, 15 and 28 hours respectively. In contrast, when these conditions were attempted by us, a DS of only 0.14, 0.25 and 0.38 were the result (**Scheme 3.5**).



**Scheme 3.5**

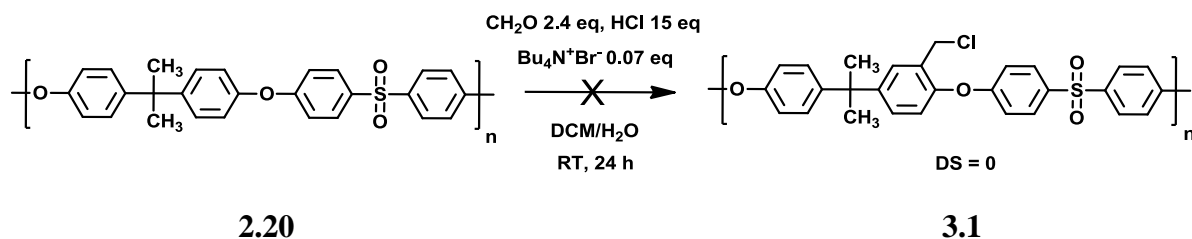
A DS of 1.20 was reported with 72 hours reaction time, with that figure rising to 1.58 when the chloromethylating mixture was increased to 10 equivalents. Interestingly, their DS finally increased to 1.85 when the catalyst loading was reduced to 10 mol %. This potentially indicates that some cross-linking may have been occurring and by lowering the catalyst loading this cross-linking was reduced to obtain a higher yield. Again, attempts at recreating these results gave a disappointing 0.58 DS (**Scheme 3.6**).



**Scheme 3.6**

A potential reason for this much reduced yield is our use of dry DCM in place of dry  $\text{CHCl}_3$  as reported. This decision was due to ease of access to dry DCM in the large quantity that was needed, under the assumption that the reaction would only be marginally affected by the switch. Regardless, the levels of chloromethylation produced by this method were too low for our purpose so other avenues were investigated.

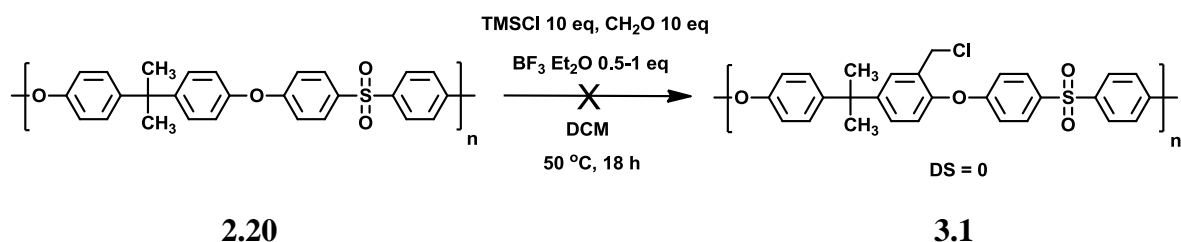
A classical method for chloromethylation of aromatics forgoes the metal catalyst in favour of refluxing in strong acid. A typical procedure involves heterogeneously refluxing the arylene with paraformaldehyde and a mixture of concentrated  $\text{HCl}$ , 85%  $\text{H}_3\text{PO}_4$  and glacial acetic acid.<sup>15,16</sup> These conditions are unsuitable for the needed functionalisation of PSF as they tend to give poor yields and there is the potential for the strong acidic media to degrade the polymer chains. It is possible that the use of a phase transfer catalyst may allow the reaction to happen homogeneously and thus under milder conditions. Given *et al.*<sup>17</sup> used tetrabutylammonium bromide as the phase transfer catalyst to afford chloromethylation under ambient conditions to produce the product in high yields on a large scale. Disappointingly, the conditions had no effect when applied to PSF (**Scheme 3.7**).



Scheme 3.7

Due to the propensity to cross-link, forcing conditions cannot be applied to the reaction to increase the yield. However, it may be possible to improve the reaction by using a less reactive catalyst, or rather a catalyst which less readily facilitates the cross-linking side reaction. The hope being that an alternative catalyst may tolerate a higher loading or a higher concentration of PSF in solution.

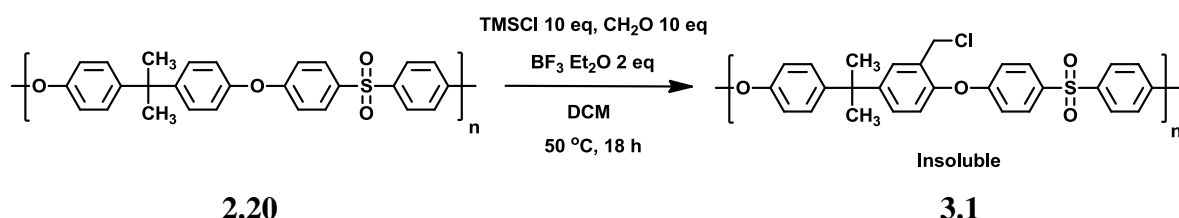
Initially  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  was chosen, due to the lack of literature precedence of it catalysing this reaction. Based on the conditions by Avram *et al.*,<sup>11</sup> 10 equivalents of chloromethylating mixture (1:1  $\text{TMSCl}$ /paraformaldehyde) were added to PSF in the minimum amount of solvent and refluxed in a sealed vessel for 18 hours. Catalyst loadings of 0.5 and 1 equivalent were used, but both failed to react (**Scheme 3.8**).



Scheme 3.8

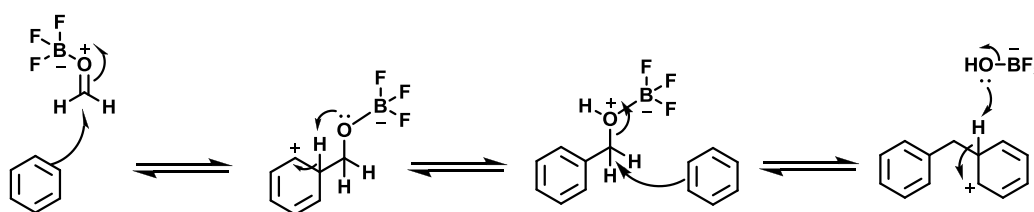
Interestingly, when the catalyst loading was increased to 2 equivalents, an insoluble product, presumably cross-linked polymer was formed (**Scheme 3.9**). This arguably shows that  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  favours forming the methylene bridges over catalysing the

chloromethylation reaction, potentially due to its relatively weaker Lewis acidity compared with other catalysts.



**Scheme 3.9**

This hypothesis was also put forward by Ogoshi *et al.*<sup>18</sup> who used BF<sub>3</sub>·Et<sub>2</sub>O in conjunction with paraformaldehyde to facilitate the creation of methylene bridges for the formation of calixarenes *via* condensation. When the condensation was attempted with the stronger Lewis acids FeCl<sub>3</sub>, AlCl<sub>3</sub> and SnCl<sub>4</sub>, linear chains quickly formed rather than the much more thermodynamically stable calixarene, indicating their increased activity, whereas the stable BF<sub>3</sub>·Et<sub>2</sub>O adduct remained until condensation occurred. **Scheme 3.10** shows a postulated mechanism for the BF<sub>3</sub>·Et<sub>2</sub>O mediated condensation/cross-linking reaction with aryl groups and paraformaldehyde.



**Scheme 3.10**

It was established that the strong Lewis acid SnCl<sub>4</sub>, whilst giving good levels of chloromethylation promoted the cross-linking reaction too strongly, whereas the weak Lewis acid BF<sub>3</sub>·Et<sub>2</sub>O did not promote the chloromethylation reaction strongly enough and solely promoted the cross-linking reaction. Therefore it seemed prudent to investigate



catalysts possessing a moderate Lewis acid strength. It was hoped that a slight reduction in Lewis acidity would mildly reduce the ability of the catalyst to chloromethylate compared to  $\text{SnCl}_4$  yet would greatly reduce the activity for the cross-linking reaction, thus resulting in a greater overall yield.

Daly *et al.*<sup>2</sup> investigated a range of Lewis acid catalysts for their ability to catalyse the chloromethylation of polyarylene ether sulfones such as PSF. They determined the following reactivity series (**Figure 3.3**).



**Figure 3.3:** Reactivity series of Lewis acid catalysts.

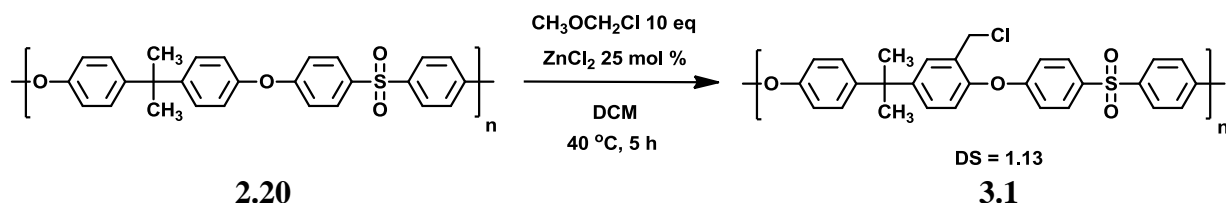
$\text{ZnCl}_2$  was the obvious next choice to investigate as a catalyst, with it showing less overall activity than  $\text{SnCl}_4$ .

B. Wang *et al.*,<sup>19</sup> similarly to Avaram *et al.*,<sup>11</sup> studied zinc catalysed chloromethylation and investigated the effect of varying reaction conditions on yield and potential cross-linking. PSF concentration was set at 10% in DCM, a much higher concentration than previously used and one which would cause cross-linking with  $\text{SnCl}_4$ . The addition of the chloromethylating reagent was also altered; 2.5-10 equivalents of MOMCl was mixed with 10-40 mol % of  $\text{ZnCl}_2$  to form a pre-catalyst, which was added dropwise to the stirred polymer solution and gradually heated to 40 °C. They noted that the reaction proceeded rapidly up until 5 hours whereupon the rate of chloromethylation rapidly decreased. CMPSF was produced with a DS between 0.5 and 1.5 and perhaps surprisingly there was no mention of cross-linking.

A similar study by G. Wang *et al.*<sup>20</sup> investigated the relationship between reaction temperature and yields. They found that whilst the yield increased when the temperature was raised, temperatures of 60 °C or higher caused cross-linking even in short reaction times. It is interesting to note that during both studies the chloromethylating agent was

added dropwise, so this is perhaps another strong factor in lowering the level of cross-linking.

From this information, we attempted the following reaction (**Scheme 3.11**) with pre-catalyst formation as shown by B. Wang *et al.*<sup>19</sup> We achieved a polymer chloromethylated to a DS of 1.13 after only 5 hours; a huge improvement on the previous methods.



**Scheme 3.11**

Initially this seemed an excellent method, quickly and cleanly giving a highly substituted polymer. However, upon attempting to scale up the reaction it became apparent that there were some major difficulties. As mentioned in section 2.4.3.2, 20 g is the minimum amount of PSF needed to feasibly make hollow fibres. On a 20 g scale of the reaction, 40 g of MOMCl would be required. This is not only a problem due to the relatively high cost of the reagent, but due to the aforementioned carcinogenic toxicity. Previous methods attempted to minimise exposure time by generating the chloromethylating reagent *in situ*, whereas pre-catalyst formation and dropwise addition in this method greatly increases exposure time, even if a paraformaldehyde/TMSCl system is used.

With the inability to easily scale the reaction up, this line of research was halted.

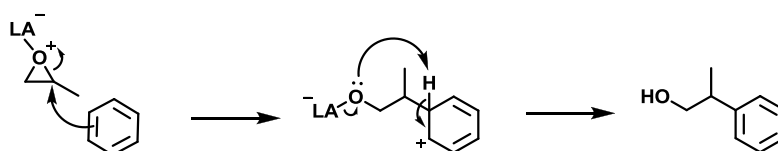
### 3.3.4 Conclusion

The general problem with the chloromethylation reaction is the need for very specific reaction conditions; forcing conditions such as high concentration, catalyst loading or temperatures cannot be applied to increase reaction yields due to the cross-linking side reaction. This necessitates the use of strict conditions and a large excess of toxic chloromethylating reagents, which is not desirable.

A possible solution is to change the functional group we are attaching to one incapable of, or at least has a much lower propensity, to cross-link. This would allow stronger conditions to be used to give a higher degree of substitution without the fear of cross-linking. In addition, the reaction would ideally use less toxic reagents to reduce the risk of exposure on the large scale chemistry that is required.

### 3.4 Epoxide Ring Opening

With the need for a functional group which would not cross-link, epoxides were investigated. Similarly to the chloromethylation reagents, epoxides undergo Friedel-Crafts type Lewis acid promoted reactions with arenes (**Scheme 3.12**).

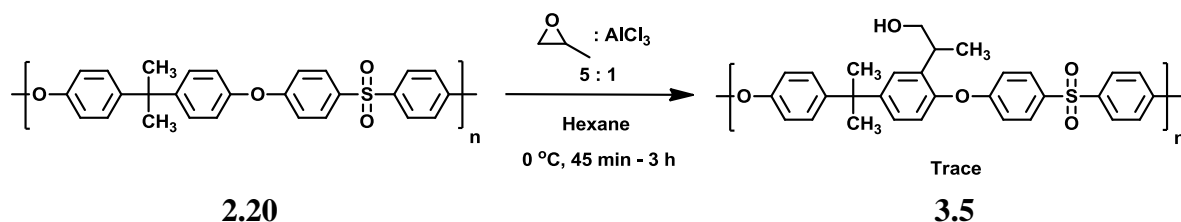


**Scheme 3.12**

Unlike chloromethylation, the product formed is much less reactive than the starting epoxide so any kind of competing reaction is much less likely to occur. The reaction gives a polymer functionalised by an ethyl tethered primary alcohol, which is a useful functionality in its own right, but can also be easily converted into an azide *via* a tosyl intermediate in order to continue the synthetic route proposed in section 3.3.2.<sup>21</sup> A potential problem however, is the prospect of reduced solubility caused by addition of the hydrophilic alcohol groups to the hydrophobic PSF backbone, as discussed in section 2.4.3.1.

Higuchi *et al.*<sup>22</sup> investigated the heterogeneous surface modification of PSF hollow fibres by dipping them into a mixture of propylene oxide,  $\text{AlCl}_3$  and hexane for up to 10 minutes. The functionalisation itself wasn't quantified, but the resultant fibres were found to have reduced flux and increased rejection of polyethylene glycol 6000 (PEG).

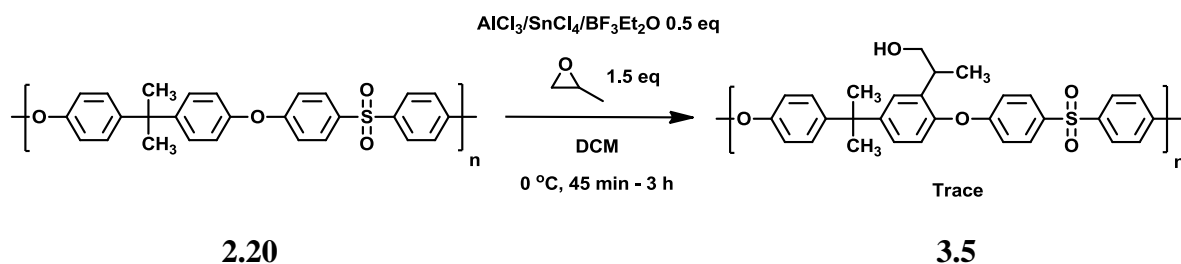
Following this procedure, using a 5:1 ratio of propylene oxide to  $\text{AlCl}_3$  in the minimum amount of hexane (**Scheme 3.13**), we achieved very minor heterogeneous functionalisation of PSF hollow fibres, as shown by disruption in the aromatic region of the  $^1\text{H}$  NMR. Due to the functionalisation only occurring at the surface of the fibre, a scalpel blade was used to remove the top layer of the fibre and this removed layer was analysed.



Scheme 3.13

Even increasing reaction times from the reported 10 minutes to 3 hours only resulted in minimal product formation. As this was a heterogeneous surface modification it is perhaps not unsurprising that the degree of substitution was extremely low. Equally the poor solubility of  $\text{AlCl}_3$  in hexane was probably another limiting factor.

In order to improve the DS, the reaction conditions were changed to a homogenous system and  $\text{AlCl}_3$ ,  $\text{SnCl}_4$  and  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  were investigated as catalysts (**Scheme 3.14**). However, these conditions failed to improve the reaction.



Scheme 3.14

Although increasing temperature, reaction time or amount of reagents used would almost certainly increase the DS of the reaction, it is not known whether the DS could be increased high enough for our purposes or if the increase needed would be feasible. Rather than investigate this, the existence of literature precedence<sup>23-25</sup> showing the use of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  to promote organolithium epoxide ring opening reactions at high yields and under relatively mild conditions suggested an easier route to the desired polymer was available. Therefore, the solely Lewis acid promoted methodology was abandoned in favour of investigating the organolithium based reaction. The organolithium epoxide ring opening functionalisation of PSF is discussed in section 4.5.

### 3.5 Formylation

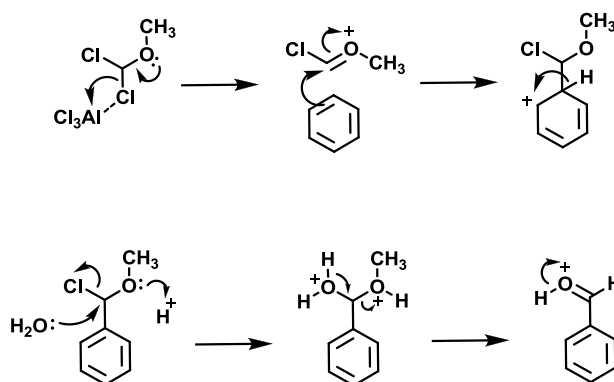
Aldehydes are another functional group that could potentially be appended to PSF *via* electrophilic aromatic substitution as they react readily with a variety of nucleophiles. Reductive amination is an attractive route post formylation which would give strong, yet flexible amine linkers between the polymer and the carrier. Aldehydes are also much less hydrophilic than the hydroxyl groups produced by the previously mentioned epoxide reactions, therefore the solubility of the produced PSF should not be affected.

There are numerous aromatic formylation reactions and their suitability for making formylated PSF varies between them.<sup>26</sup> Out of the common formylation techniques, Reimer-Tiemann<sup>27</sup> formylation almost exclusively formylates phenols, Duff<sup>28</sup> formylation tends to require activated aromatics or strong acids to achieve acceptable yields and Gatterman-Koch<sup>29</sup> formylation requires high pressures of highly poisonous carbon monoxide.

On the other hand, both Reiche formylation and Vilsmeier Haack formylation seemed suitable for the task with mild reaction conditions, good yields and relative safe reagents, and as such were investigated.

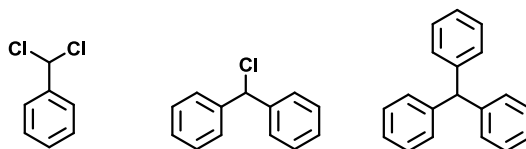
### 3.5.1 Reiche Formylation

Reiche formylation is a very similar reaction to the aforementioned chloromethylation reaction, but utilises dichloromethyl methyl ether (DCME) in place of MOMCl. This generates a different Lewis acid complex, which upon reacting with an aryl group gives a methoxthychloromethyl group, which easily hydrolyses to the target aldehyde upon work up of the reaction. A proposed mechanism for the formylation is shown in **Scheme 3.15**.<sup>30,31</sup>



**Scheme 3.15**

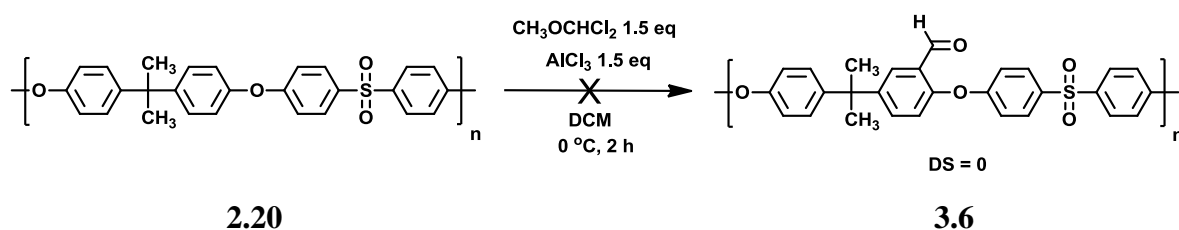
There was concern that due to the similar mechanism of this reaction and chloromethylation, the Reiche formylation could also potentially suffer from the same cross-linking issues. Interestingly, Yakubov *et al.*<sup>31</sup> showed that variation in the ratio of reactants as well as change in steric bulk of the arene, produced a range of side products including dichloromethyl,  $\text{CHCl}$  cross-linked and  $\text{CH}$  tri-crosslinked products (**Figure 3.4**).



**Figure 3.4:** Potential side products of Reiche formylation.

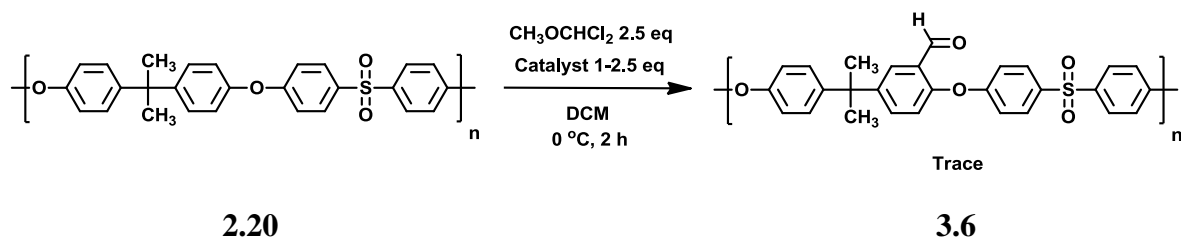
However, the overall literature precedence<sup>32-34</sup> for the transformation showed it to give high degrees of substitution. Most importantly, these results were achieved after short reaction times and under ambient temperatures, which suggested that the side-reactions could be avoided under the right conditions. It should also be noted that DCME, unlike MOMCl, is not carcinogenic and shows minimal toxicity whilst also costing significantly less, thus making its large scale use feasible.

Initially the reaction was attempted using dropwise addition of DCME to a stirred solution of PSF and AlCl<sub>3</sub>, dissolved in the minimum amount of DCM and chilled to 0 °C. After 2 hours the reaction was simultaneously quenched and hydrolysed by pouring the reaction mixture into ice. The conditions unfortunately failed to produce any product (**Scheme 3.16**).



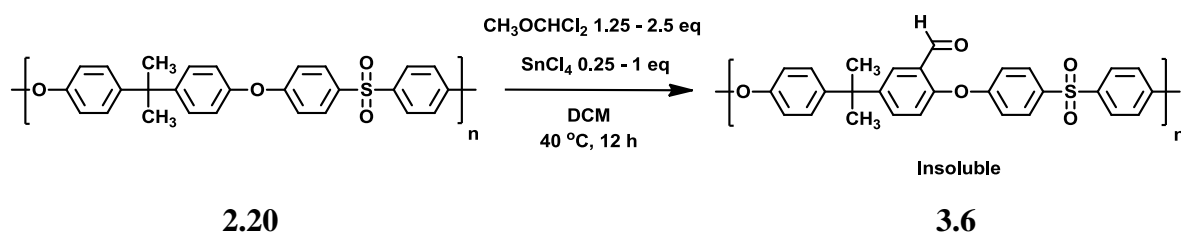
**Scheme 3.16**

In an attempt to improve the reaction, equivalents of TiCl<sub>4</sub>, AlCl<sub>3</sub>, ZnCl<sub>2</sub> and SnCl<sub>4</sub> were varied alongside a higher loading of DCME, regrettably with poor results (**Scheme 3.17**).



Scheme 3.17

These results indicated that the reaction is much more difficult to achieve on PSF than the range of molecules functionalised in the literature. As such, reaction temperature and time were then increased to try and improve the reaction (**Scheme 3.18**).



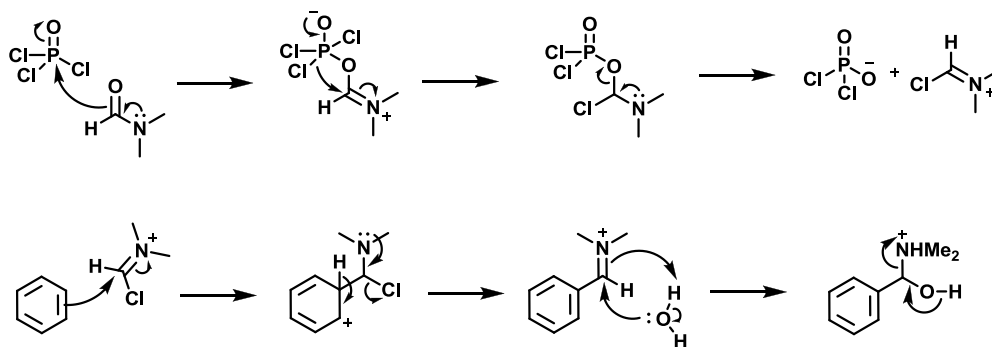
Scheme 3.18

The result of the reflux was a brittle, black, insoluble product. Evidently the elevated conditions caused undesired side reactions. Assuming that the increased temperature facilitated both the formylation and cross-linking to an extent, then optimisation becomes difficult, a problem we discussed with the chloromethylation reaction. It is possible that there exists an optimal set of conditions, potentially involving increased dilution, catalyst pre-mixing or simply changing the reactant equivalents further. However, the lack of anything other than trace amounts of products in the reactions attempted, especially in relation to the results given by literature, suggests that the reaction is unsuitable to functionalise PSF. Therefore no further optimisation of these conditions was attempted.



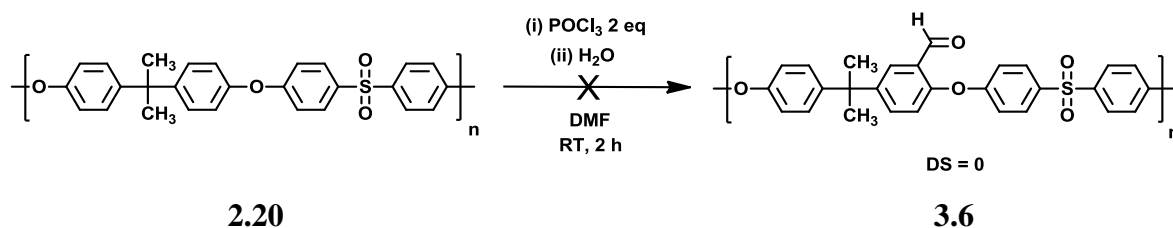
### 3.5.2 Vilsmeier Haack Formylation

The Vilsmeier Haack reaction is a mild formylation technique for a range of aromatic compounds. It favours activated species, but is also able to functionalise simpler aromatics under suitable conditions.<sup>35-37</sup> Unlike the previous functionalisations investigated so far, it is not metal mediated. The active species is a chloroiminium complex, usually formed by the reaction of POCl<sub>3</sub> with DMF. Upon reaction with an arene the resultant iminium is easily hydrolysed to the target aldehyde, similarly to the final step of Reiche formylation. The predicted mechanism is shown in (Scheme 3.19).



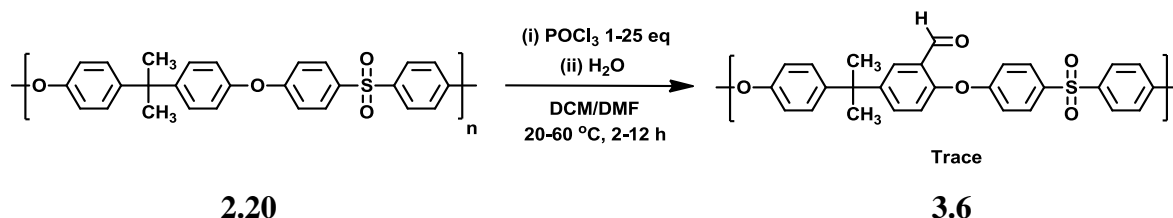
Scheme 3.19

For our initial attempts at the reaction we chose relatively mild conditions (Scheme 3.20). Two equivalents of POCl<sub>3</sub> were added dropwise to a cooled solution of PSF dissolved in DMF. The reaction was quenched by addition of ice water after 2 hours. These conditions did not produce any of the desired product, perhaps not unsurprisingly as our previous work so far has indicated that PSF is not particularly reactive under mild conditions.



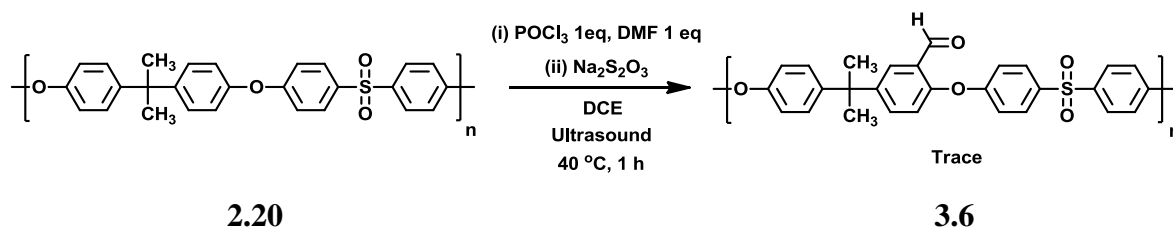
Scheme 3.20

From this starting point a range of variables were investigated. PSF has low solubility in DMF and thus requires a relatively large dilution. Therefore a mixed DCM/DMF system was tried. Rather than forming the formylating agent *in situ*, it was added directly by pre-mixing DMF with POCl<sub>3</sub> and adding the resulting solution dropwise. Finally, the reaction time, temperature and the equivalents of formylating reagent were investigated. These changes did not elicit the desired results, even with 25 equivalents of formylating agent and moderate heating, only trace products were produced (**Scheme 3.21**).



Scheme 3.21

An alternative procedure proposed by Ali *et al.*<sup>35</sup> performed the reaction with DCE as the solvent under ultrasound conditions. The ultrasound technique improved the DS over equivalent thermal conditions and achieved formylation of compounds inert to the standard reaction. Unfortunately, reacting PSF under these new conditions gave poor results (**Scheme 3.22**). Only trace amounts of product was produced as shown by disruption of the aromatic region of the <sup>1</sup>H NMR.



Scheme 3.22

At this stage, a similar conclusion to that of the epoxide synthesis was reached. It may be possible to improve the reaction by further increasing reaction temperatures and time, but the severe lack of reactivity suggests the reaction is difficult.

As such, it was decided that if a formylated PSF was to be synthesised it was more likely to occur *via* organolithium chemistry and thus further investigation into formylation focused on this.

Formylation *via* organolithium reagents is discussed in section 4.7.

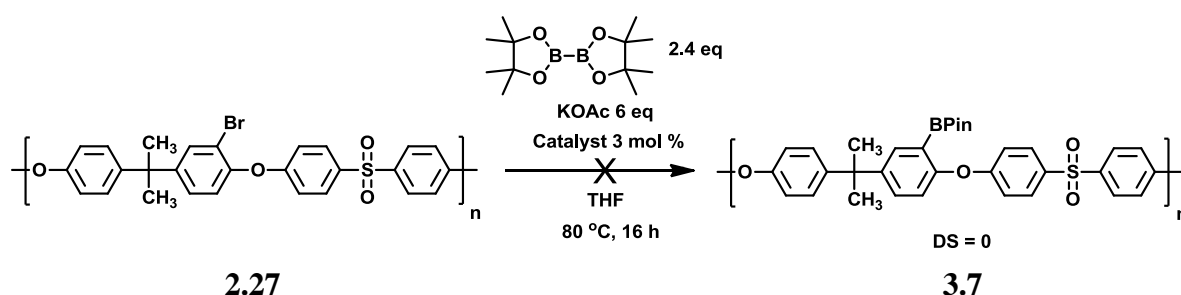
### 3.6 Suzuki-Miyaura Cross-Coupling

So far in this study, directly functionalising PSF *via* electrophilic aromatic substitution has proven extremely difficult outside of bromination, which proceeds flawlessly. Therefore it would be prudent to try and take advantage of the success of the bromination to further functionalise the polymer. Aryl bromides are known to commonly undergo two major transformations; organometallic chemistry such as the formation of Grignard reagents and Suzuki-Miyura cross-coupling type reactions.

The Suzuki reaction is one of the most widely used reactions for carbon-carbon bond formation. It is able to couple a wide range of easily available substrates, under mild conditions, tolerating other functionality and producing relatively non-toxic by-products.<sup>38,39</sup> The importance of the reaction has recently been reflected by Suzuki, along with Negishi and Heck being awarded the 2010 Nobel Prize for palladium-catalysed cross coupling reactions. Amongst its many applications, relevant to this work it has been used in both the polycondensation synthesis of polymers<sup>40,41</sup> and the modification of polymer chains.<sup>42,43</sup>

Our initial attempts at using Suzuki chemistry focused upon the reaction of dibrominated PSF **2.27** with bis(pinacolato)diboron under standard Suzuki conditions<sup>44</sup> to give directly borylated PSF **3.7**. Although this would not produce an ideal polymer, as the boron is not attached on a tether away from the polymer backbone, it would serve to be a model compound, and could potentially demonstrate some activity at separating simple compounds. It could also undergo subsequent Suzuki reactions to install more complex functionality.

Following the procedure by Todd *et al.*<sup>44</sup> a range of catalysts were investigated, including Pd(OAc)<sub>2</sub>, Pd(dba)<sub>2</sub>, Pd(PPh<sub>3</sub>)<sub>4</sub> and Pd(dppf)<sub>2</sub>Cl<sub>2</sub>, however they all performed poorly (**Scheme 3.23**).



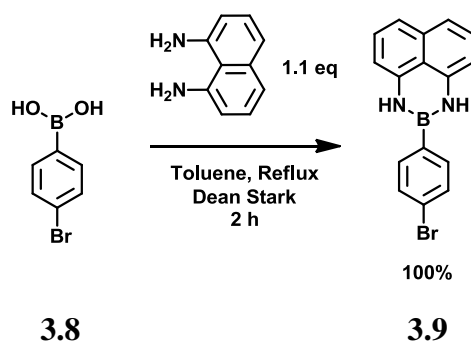
**Scheme 3.23**

Concurrently to this line of research, an organolithium based technique for synthesising **3.7** and *ortho*-sulfone isomer **3.10** was perfected, as discussed in section 4.3. This voided the need to develop this reaction further.

PSF **3.7** was investigated for its potential Suzuki coupling with aryl bromides. Normally this would not be a route to add a boron group to the polymer, as a boron containing aryl bromide would itself be Suzuki active and would compete with a homocoupling reaction. Noguchi *et al.*<sup>45</sup> developed a solution to this issue by using the 1,8-diaminonaphthalene (DAN) group to create “masked” boronic acids. The most common boronic acid protecting groups such as pinacol or neopentyl glycol are reactive to Suzuki conditions, whereas the

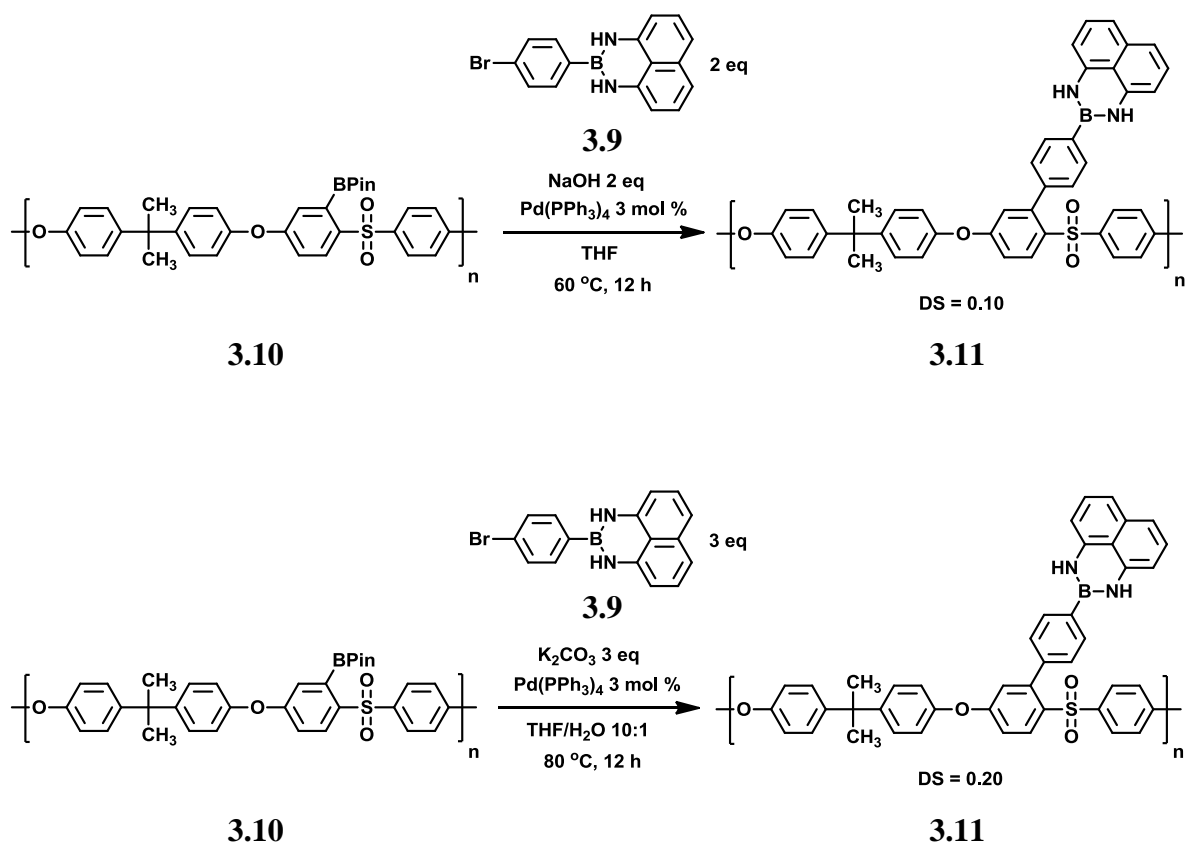
“masked” boronic acid is inert. In theory, this would allow us in to directly couple an aromatic DAN protected boronic acid to borylated PSF.

The “masked” boronic acid **3.9** was quantitatively synthesized *via* Dean Stark reflux in toluene to azeotropically remove water (**Scheme 3.24**).



**Scheme 3.24**

The coupling of the *ortho*-sulfone borylated PSF **3.10** and aryl bromide **3.9** was attempted under different conditions, but failed to produce a product with a high enough DS (**Scheme 3.25**). The reaction was monitored by the reduction of the pinacol signal in the <sup>1</sup>H NMR spectra.



Scheme 3.25

Subsequently to this research, Jo *et al.*<sup>46</sup> published a paper pertaining to the synthesis of borylated PSF *via* iridium C-H activation. Using their produced PSF **3.10**, they successfully Suzuki coupled a range of functional aryl bromides including aldehydes, alcohols and protected amines. Their conditions are identical to the ones we employed, but used a much larger 10 equivalents of the aryl bromide.

With this taken into account it's probable that the reactions in **Scheme 3.25** could be improved by greatly increasing the equivalents of the aryl bromide. The large amount of expensive boron reagents needed to achieve this however, makes the transformation economically unviable; which is a considerable issue considering neither polymer contains the desired flexible linker.

### 3.7 Aminomethylation

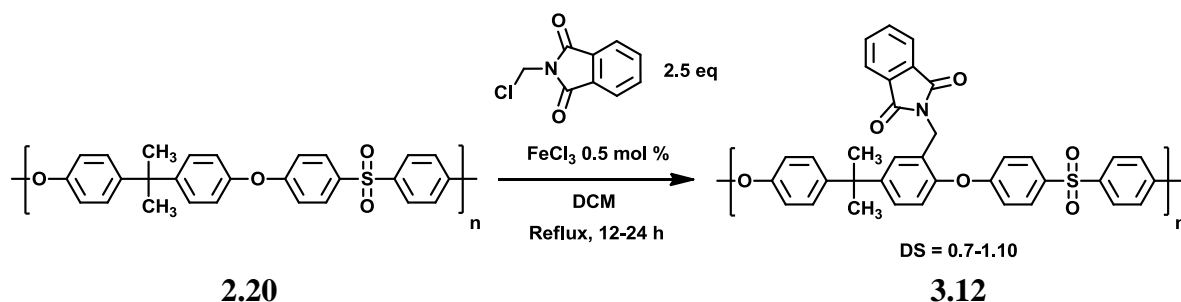
Out of the routes attempted to functionalise PSF so far, chloromethylation was the nearest to being successful, as it generally has a high enough reactivity, but suffers from debilitating cross-linking side reactions. As discussed previously, the solution to this would be to use a substrate that could undergo similar Friedel Crafts chemistry, but would be incapable of cross-linking. The difficulty comes with wanting to add a functional group that would enable further functionalisation of the polymer but would not interfere with the initial functionalisation process. The obvious solution is to use protecting group chemistry; the functional group added having its functionality masked to prevent it from competing with the modification process. Once the reaction is complete, the protecting group can be removed to give the desired reactive site. An example of this is the previously mentioned DAN-protected boronic acid **3.9** which can be used for Suzuki couplings and subsequently deprotected to reveal a free boronic acid.

#### 3.7.1 Phthalimides

A widely used protecting group strategy is to use phthalimide groups as protected amines. They are most commonly used in the Gabriel synthesis of primary amines, whereupon an alkali salt of phthalimide nucleophilically attacks an alkyl halide to give an alkyl phthalimide.<sup>47</sup> The phthalimide can subsequently be converted into a primary alkyl amine either by acid or basic hydrolysis or by the Ing-Manske reaction, which uses hydrazine to afford phthalohydrazide and the free amine.<sup>48,49</sup> Phthalimide is favoured for this task over other protected amines due to the lack of secondary and tertiary amine side products produced.

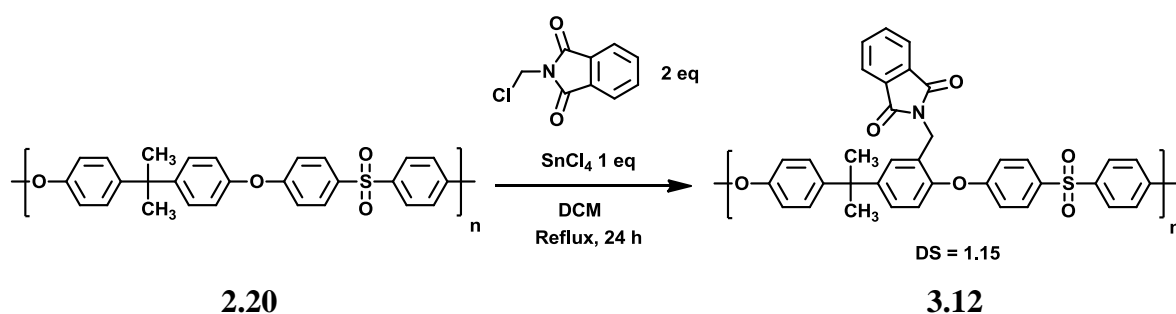
Daly *et al.*<sup>2</sup> used the Gabriel synthesis to convert chloromethylated PSF into phthalimidated PSF using potassium phthalimide. They also converted unmodified PSF directly using *N*-hydroxymethylphthalimide in concentrated trifluoroacetic acid. However, the strongly acidic conditions used resulted in a loss of molecular weight *via* chain scission, therefore the method is not suitable for producing PSF for hollow fibres. Hinke *et al.*<sup>50</sup> suggested an alternative Friedel Crafts type reaction using SnCl<sub>4</sub>, FeCl<sub>3</sub> or AlCl<sub>3</sub> to catalyse the addition of *N*-chloromethylphthalimide at high yields. The milder conditions used meant that no chain scission occurs and as such this method was investigated.

Initial conditions using  $\text{FeCl}_3$  and excess *N*-chloromethylphthalimide in DCM produced a functionalised product with a DS of 0.7 (**3.12**) after 12 hours, which rose to 1.1 after 24 hours (**Scheme 3.26**).



Scheme 3.26

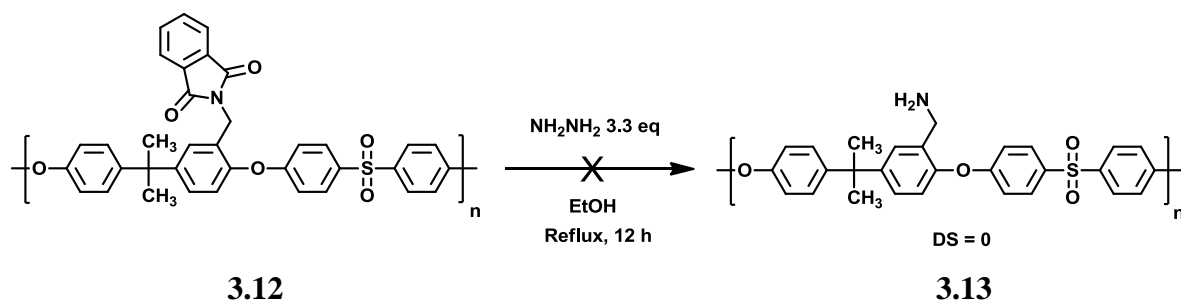
$\text{SnCl}_4$  and  $\text{ZnCl}_2$  were also investigated as catalysts. Stoichiometric amounts of  $\text{SnCl}_4$  were required to achieve similar results to  $\text{FeCl}_3$  (**Scheme 3.27**).  $\text{ZnCl}_2$  however, only gave trace amounts of product.



Scheme 3.27

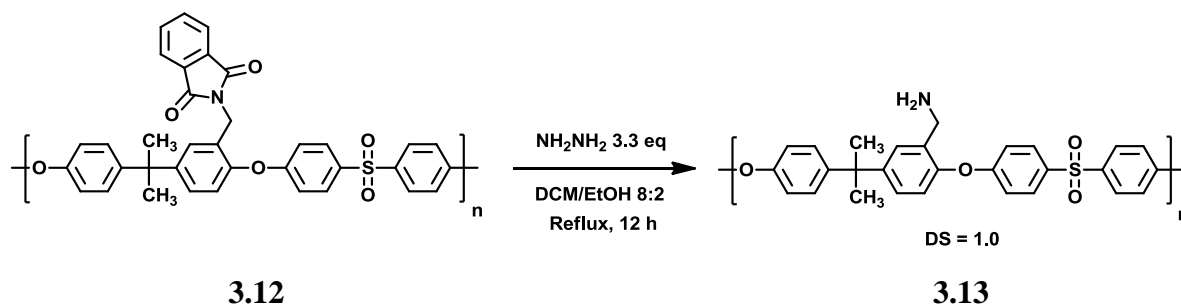
Hinke *et al.*<sup>50</sup> proposed deprotection conditions of refluxing the polymer heterogeneously in ethanolic hydrazine. When attempted on **3.12**, this failed to remove any of the phthalimide groups, a result also observed by Daly *et al.*<sup>2</sup> (**Scheme 3.28**).





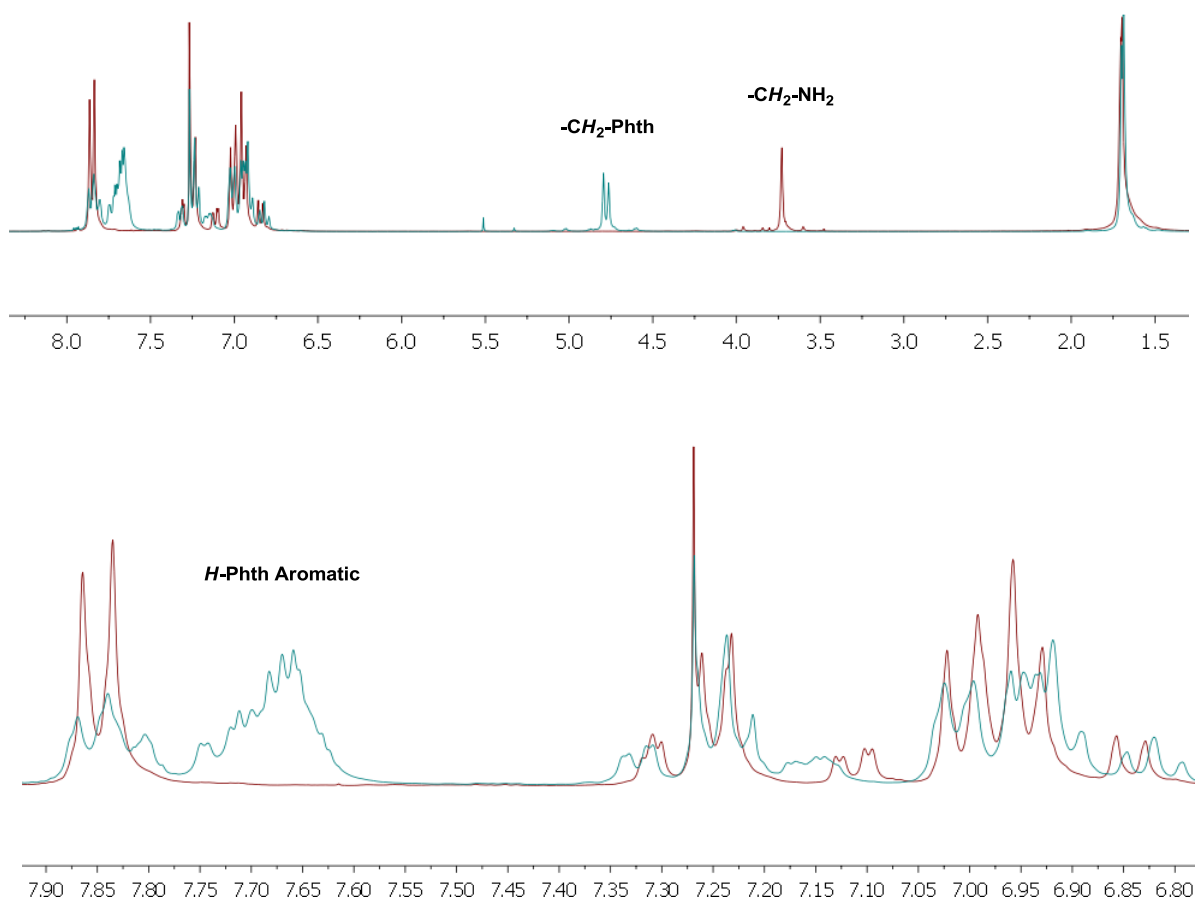
Scheme 3.28

The solution to this was to switch from a heterogeneous to a homogenous reaction using a mixed EtOH/DCM solvent system. Under these conditions, the deprotection proceeded quantitatively to afford **3.13** (Scheme 3.29).



Scheme 3.29

The deprotection can be easily identified by  $^1\text{H}$  NMR which shows that the  $\text{CH}_2$  peak adjacent to the phthalimide shifts from  $\delta 4.78$  ppm to  $\delta 3.73$  ppm upon deprotection. There is also an obvious loss of the phthalimide aromatic peaks between  $\delta 7.8$ - $7.6$  ppm (**Figure 3.5**). The product remained soluble in the usual solvents.



**Figure 3.5:** Overlay of the 300 MHz  $^1\text{H}$  NMR spectra of phthalimided and aminomethylated PSF.

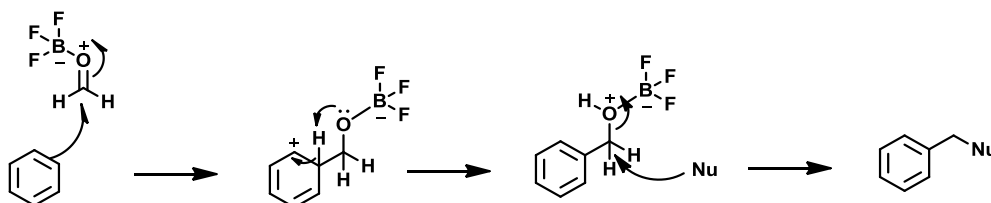
The deprotection worked perfectly on a small scale of 0.5-1 g, however, it failed upon scaling up to 7 g and 15 g, with little to no product even after 3 days and 5 equivalents of hydrazine. Increasing the equivalents of hydrazine to 10 caused the PSF to form an extremely hard insoluble lump precipitate which required dissolution in concentrated sulfuric acid to remove it from the reaction vessel. In order to try and improve the deprotection, THF and NMP were both tried as alternative solvents to DCM, and whilst they again worked for small scale deprotections, they failed upon scale up.

Phthalimide is notoriously difficult to cleanly remove so coupled with the general difficulties involved with polymer and bulk scale chemistry, it is perhaps not surprising that there were problems with the deprotection. Hydrazine is also extremely toxic and a

potential carcinogen so its large scale use should probably be avoided. Whilst the deprotection was unsuccessful, the initial functionalisation proceeded excellently, in a high degree of substitution and with no side products, as hoped for using a protecting group strategy. Therefore a solution could be to replace the phthalimide with a more labile protecting group. At this point however, an alternative route was discovered.

### 3.7.2 Trichloroacetamides

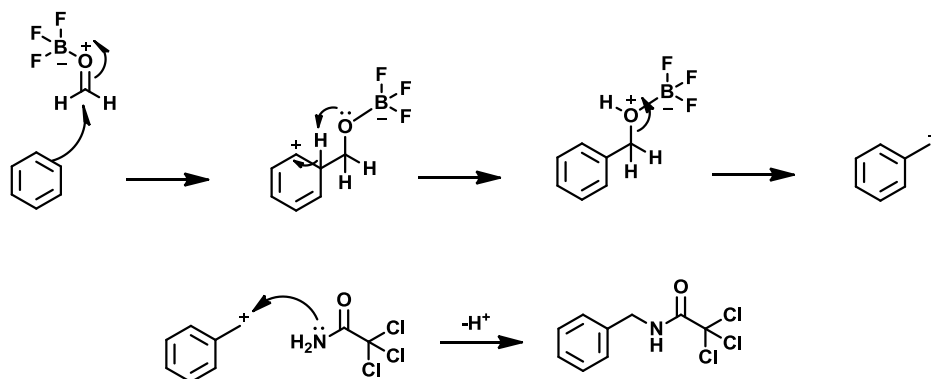
As discussed in section 3.3.3,  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  will catalyse the cross-linking reaction of paraformaldehyde and aryl groups. The final intermediate of the postulated mechanism in **Scheme 3.10** is an activated benzyl alcohol which is then nucleophilically attacked by another aryl group to give a methylene bridged biaryl. In theory, as shown in **Scheme 3.30**, a stronger nucleophile or one in a higher concentration than the aryl groups, could replace the second aryl group in the final step of the reaction to give the nucleophile appended at the benzyl position.



**Scheme 3.30**

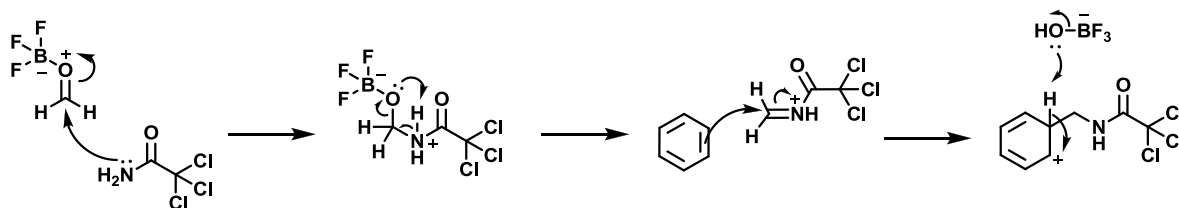
It is possible that a protected amine could be used as this nucleophile. This theory is supported by the work of Atanassova *et al.*<sup>51</sup> who used trichloroacetamide as the nucleophilic species alongside  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  and paraformaldehyde to form benzyl trichloroacetamides. In reality, amides and especially trichloroacetamides are very poor nucleophiles meaning the mechanism postulated in **Scheme 3.30** is probably incorrect, with trichloroacetamide unlikely to facilitate an  $\text{S}_{\text{N}}2$  type reaction. However, the reaction could potentially follow an  $\text{S}_{\text{N}}1$  type mechanism (**Scheme 3.31**), as the intermediate benzyl

carbocation is a much stronger electrophile than the activated benzyl alcohol. This could compensate for the poor nucleophilicity of trichloroacetamide.



**Scheme 3.31**

Alternatively, a Mannich type mechanism could occur, such that an iminium forms as the active electrophile in the system (**Scheme 3.32**).

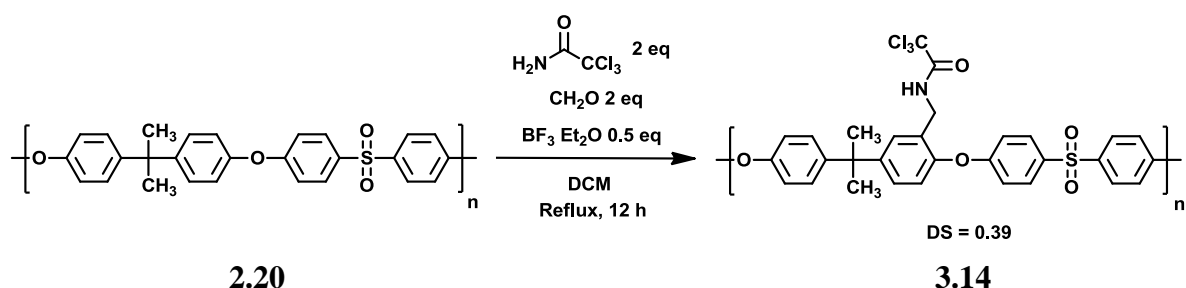


**Scheme 3.32**

A patent by Kazuo *et al.*<sup>52</sup> used similar chemistry, in the acid catalysed addition of *N*-methylol- $\alpha$ -chloroacetamide to PSF in nitrobenzene to give chloroacetamidomethyl appended PSF. Whilst successfully giving the target in high yields, the large amount of concentrated sulfuric acid used (200 ml per 5 g of PSF) will almost certainly lead to some

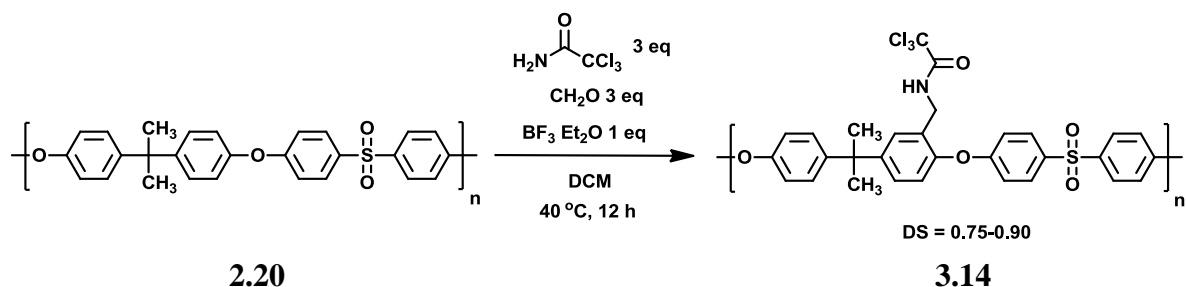
degradation of the polymer. Therefore it was decided to investigate the comparatively milder  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  catalysed trichloroacetamide routes.

Initially we refluxed PSF in a minimum amount of DCM with 2 equivalents of paraformaldehyde and trichloroacetamide and 0.5 equivalents of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ . As shown in **Scheme 3.33** this gave a respectable level of functionalisation.



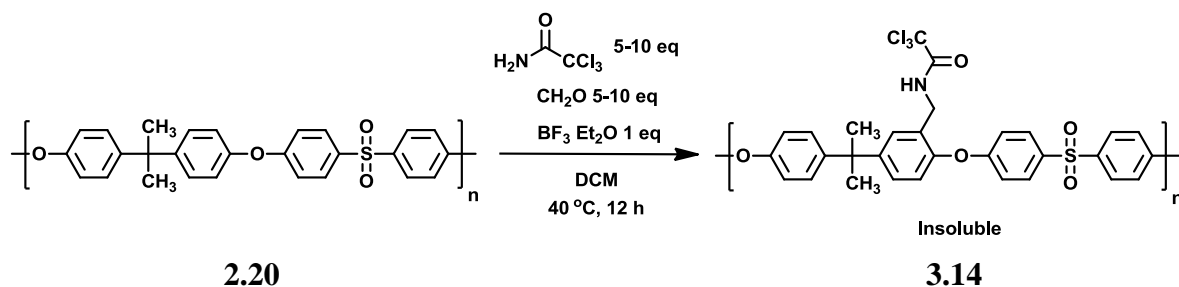
**Scheme 3.33**

In an attempt to improve the DS, the equivalents of reactants were increased by 50% and the catalyst loading doubled. The system was also changed from a standard reflux to reacting in a boiling tube. This greatly improved the DS to a level acceptable for our needs (**Scheme 3.34**).



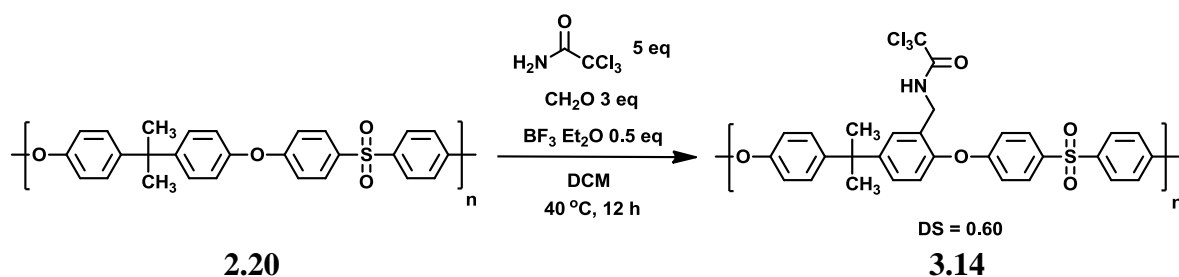
**Scheme 3.34**

Further increasing the amount of trichloroacetamide and paraformaldehyde to 5 or 10 equivalents led to an insoluble precipitate, presumed to be the cross-linked side product (Scheme 3.35).



Scheme 3.35

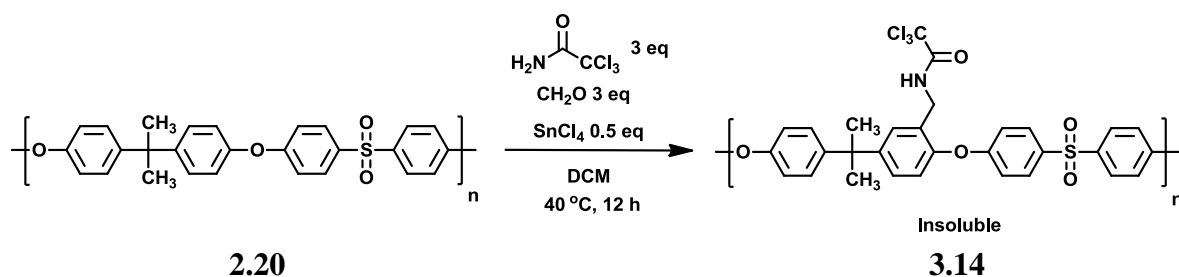
From this we can assume that the level of cross-linking is proportional to the amount of paraformaldehyde used. It was postulated that by using excess trichloroacetamide in relation to paraformaldehyde, the DS could be increased whilst suppressing the side reaction. Using 3 equivalents of paraformaldehyde and 5 equivalents of trichloroacetamide afforded the desired polymer with a DS of 0.6 as shown in Scheme 3.36.



Scheme 3.36

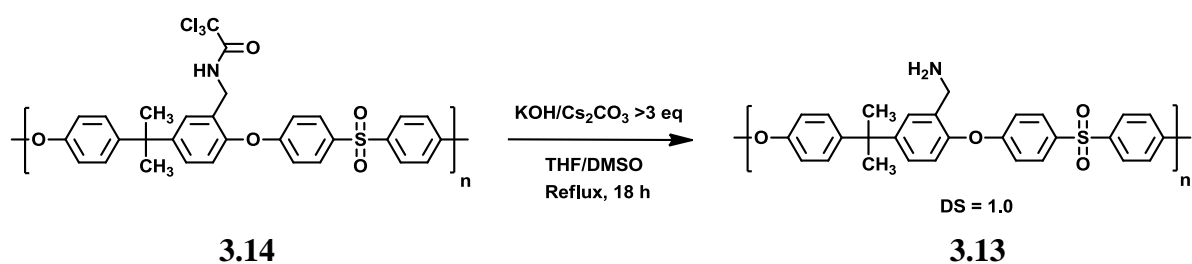
Although this is an improved DS over the initial conditions used in **Scheme 3.33**, it is not as effective as the conditions described in **Scheme 3.34**. Therefore the optimal conditions arrived at are 3 equivalents of both paraformaldehyde and trichloroacetamide and 1 equivalent  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ .

$\text{SnCl}_4$  was also investigated as a catalyst for the reaction, but only the cross-linked product was produced, even with low amounts of paraformaldehyde (**Scheme 3.37**).



Scheme 3.37

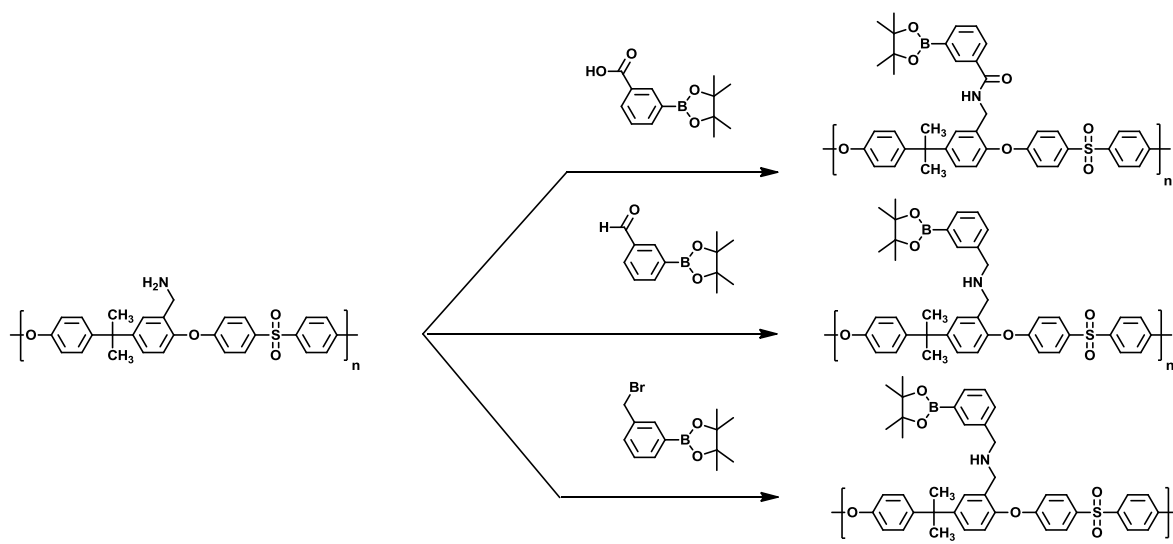
Deprotection of the trichloroacetamide proceeded quantitatively *via* refluxing PSF **3.14** and base, either with KOH in THF<sup>53</sup> or  $\text{Cs}_2\text{CO}_3$  in DMSO<sup>54</sup> (**Scheme 3.38**).



Scheme 3.38

This method proved to be particularly useful as it produces a primary amine functionalised PSF quickly and cleanly over 2 steps. It is envisaged that this amine functionalised PSF can be used in a variety of further reactions in order to achieve our boronic acid appended

polymer. As illustrated in **Scheme 3.39**, simple routes include reaction with alkyl halides, reductive amination with aldehydes and peptide coupling with carboxylic acids, to give a polymer with a boronic acid carrier appended by a flexible linker.



**Scheme 3.39**

### 3.8 Conclusion and Future Work

In this chapter we investigated a range of electrophilic aromatic substitution mediated routes to functional PSF. Considering the bromination of PSF as the model reaction it was hoped that other reactions giving more complex functionality would perform similarly.

Chloromethylation, epoxide ring opening, formylation and Suzuki coupling type reactions were all attempted to provide a range of functionality, but were met with limited success. Degrees of substitution were lower than warranted and unwanted side-reactions were a significant problem. This was especially frustrating when reactions that work on similar monomeric species failed to effect the desired change when applied to PSF. This indicates that issues specific to polymer chemistry as discussed in section 2.4.3 such as solubility or cross-linking were affecting the reactions. In hindsight, whilst extensive investigation into



the type and amount of reactants used for the reactions was undertaken, reaction temperature and length have more scope for investigation. This is especially relevant to the Vilsmeier Haack formylation where further research indicates reactions often require temperatures greater than 100 °C. However, these transformations were all eventually completed successfully using organolithium chemistry, under mild conditions and to excellent yields as described in chapter 4. This means that further research would only be required in the event that organolithium chemistry was not suitable, which could possibly be the case in industrial scale up.

Aminomethylation using *N*-chloromethylphthalimide was successful at functionalising the polymer, but proved inconveniently stubborn to deprotect and required the use of a large amount of highly toxic hydrazine. Again, further research on the matter has suggested alternate deprotection conditions that may well prove successful (Warshawsky *et al.*<sup>55</sup>), but the development of the trichloroacetamide route as an alternative provides an easier and safer deprotection route to the desired amine, one much superior to previous literature conditions.

With the successful synthesis of functionalised PSF finally achieved in the form of aminomethylated PSF, attachment of the boronic acid carrier needs to be investigated. It is assumed that this attachment would be trivial, with solubility being the only concern. Once this boronic acid carrier attachment is optimized, this finished polymer will then be ready for spinning into hollow fibres, where its sugar separating properties can be investigated.

### 3.9 References

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## Chapter 4 : Functionalisation of Polysulfone *via* Organolithium Reagents

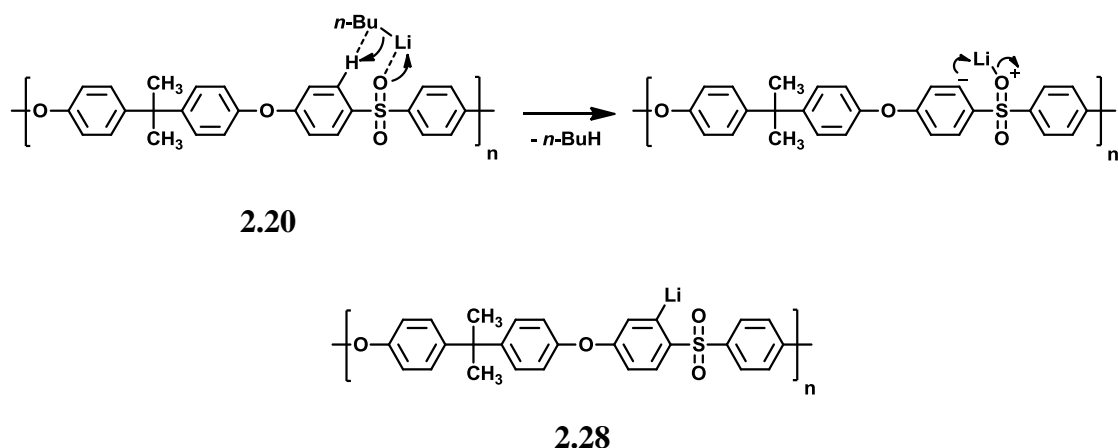
### 4.1 Introduction

This chapter discusses the routes and attempts undertaken to functionalise PSF *via* organolithium reagents.

### 4.2 Organolithium Chemistry

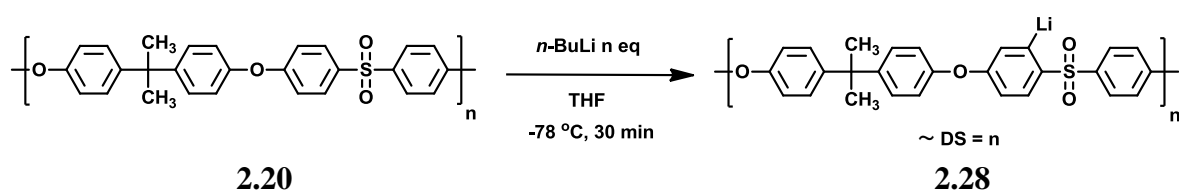
Organolithium compounds are popular and versatile reagents. They are able to act both as strong nucleophiles and strong bases and hence they are employed in a wide range of chemistry.<sup>1,2</sup> Prominent examples include the use of lithium diisopropylamide (LDA) as a sterically hindered strong base for the deprotonation step in the formation of enolates<sup>3</sup> and *n*-butyllithium (*n*-BuLi) as an initiator in the step-grow polymerisation of alkenes.<sup>4</sup> Extensive research has been undertaken by Guiver *et al.*<sup>5-9</sup> into the use of organolithium as a means to functionalise PSF, discovering *n*-BuLi as a suitable reagent for clean and quantitative functionalisation.

It was found that dropwise addition of *n*-BuLi, to a stirred solution of PSF in anhydrous THF under an inert atmosphere and cooled between -50 °C and -90 °C (dependent on subsequent reactions) resulted in lithiated polymer **2.28**. The deprotonation and subsequent lithiation occurs exclusively *ortho* to the sulfone moiety due to the strong chelating and directing effect the sulfone has with *n*-BuLi (**Scheme 4.1**).



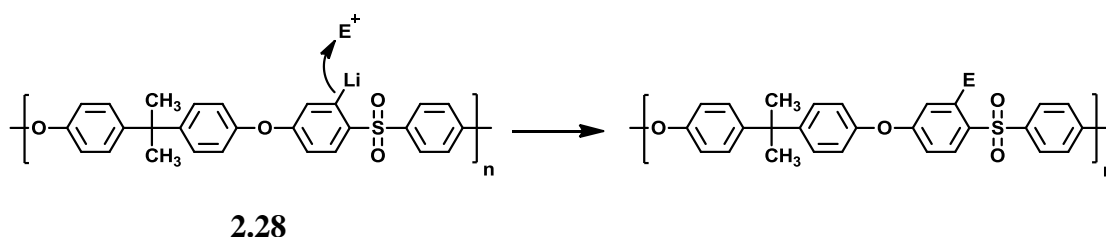
Scheme 4.1

The reaction also occurs almost quantitatively, allowing the amount of *n*-BuLi added to accurately control the reaction yield. As such, our standard lithiation is shown in **Scheme 4.2**. Interestingly, the solution changes colour relative to the amount of lithium added, initially turning green, then to yellow and eventually a dark red colour as lithiation increases.



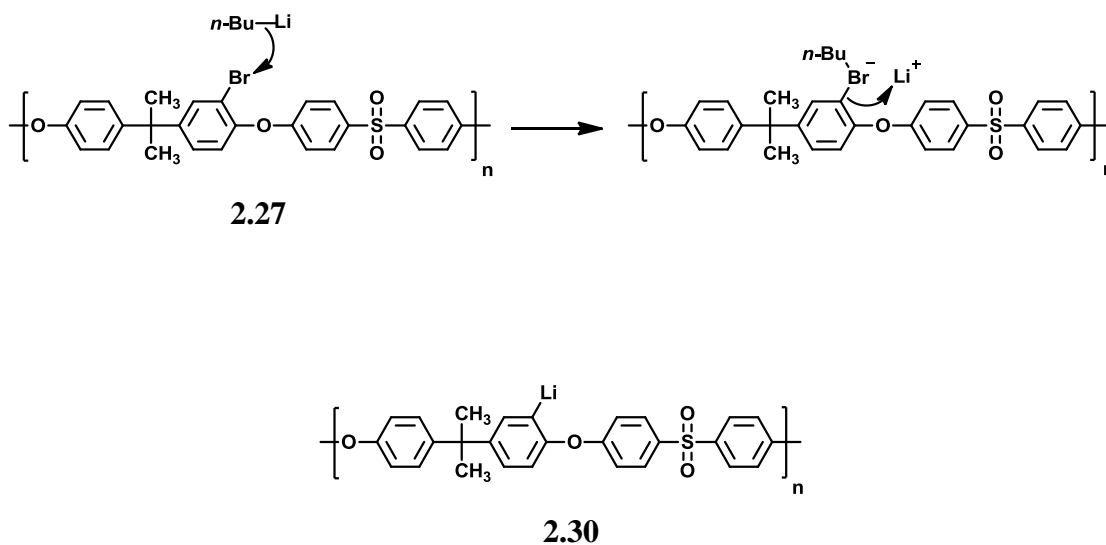
Scheme 4.2

This lithiated PSF is highly reactive and cannot be isolated, but can be used *in situ* to facilitate electrophilic substitution. Upon rapid addition of an excess of a wide range of electrophiles, followed by precipitation of the polymer into a suitable solvent such as methanol or ethanol, PSF functionalised by the electrophile is quantitatively achieved (**Scheme 4.3**).



Scheme 4.3

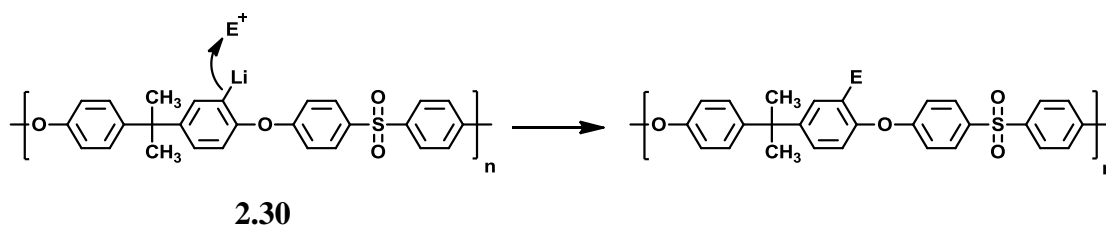
Alternatively, if brominated PSF **2.27** is used in place of PSF **2.20**, a competing halogen-lithium exchange preferentially occurs. This typically proceeds *via* an “ate complex” intermediate before generation of *ortho*-ether lithiated PSF **2.30** and butyl bromide (Scheme 4.4).



Scheme 4.4

The halogen-lithium exchange occurs much more readily than the *ortho*-sulfone deprotonation. This results in the vast majority of the product being *ortho*-ether lithiated PSF **2.30**, although small amounts of *ortho*-sulfone product may occur. It should be noted that the potential colour change observed when lithiation occurs is obscured by the deep

brown colour produced by the released bromide. The *ortho*-ether lithiated polymer can then react with electrophiles in the same manner as **2.28** to produce the *ortho*-ether isomer (Scheme 4.5).



Scheme 4.5

Lithiation is an ideal technique owing to its ability to quickly and cleanly afford a range of differently functionalised polymers where the degree of substitution is accurately controlled by stoichiometry. As such, a large portion of this research was focused on investigating its use towards the synthesis of a highly functionalised boronic acid polymer.

### 4.3 Direct Borylation

Borylation of aryllithium species is a transformation that has been used extensively in literature across a wide range of substrates.<sup>10-12</sup>

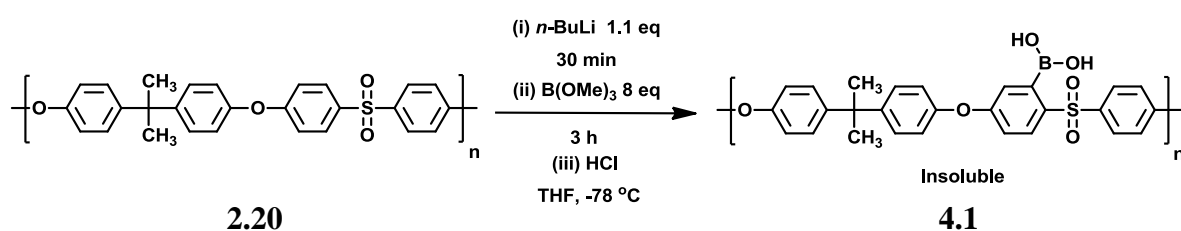
The general reaction involves quenching of a generated aryllithium by addition of an electrophilic borate compound, commonly trimethyl borate or triisopropyl borate, to give an aryl boronic acid upon hydrolytic workup (Scheme 4.6).



Scheme 4.6

Although this type of reaction would not generate the desired tethered carrier it would create a model compound potentially capable of performing simple separations. It could also be used in Suzuki coupling reactions, as discussed in section 3.6.

Initially standard conditions were attempted. PSF was lithiated with a slight excess of *n*-BuLi added at a rate of 30 mLh<sup>-1</sup> by syringe pump, followed by swift addition of a large excess of B(OMe)<sub>3</sub>. It was hoped this would achieve a polymer borylated with a DS of around 1.0, however an insoluble polymer was produced (**Scheme 4.7**).

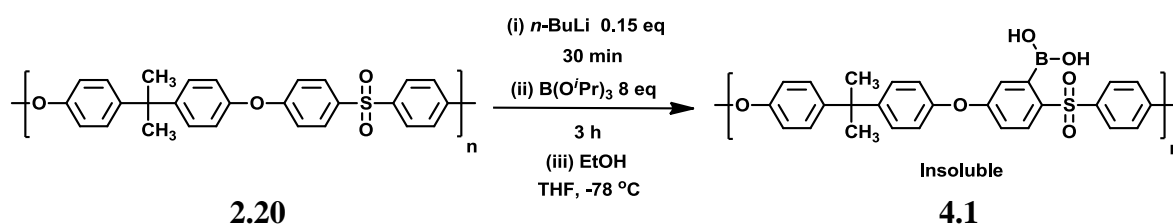


**Scheme 4.7**

It can be postulated that there were two possible reasons why the reaction failed when applied to PSF; either the reaction was successful, but the hydrophilic nature of the free boronic acids gave an insoluble product, or there were side reactions, potentially cross-linking caused by a reaction of a PSF bound boronic acid with another lithiated PSF site or the formation of so-called “BOB” complexes of bridging oxygens between different boronic acids.

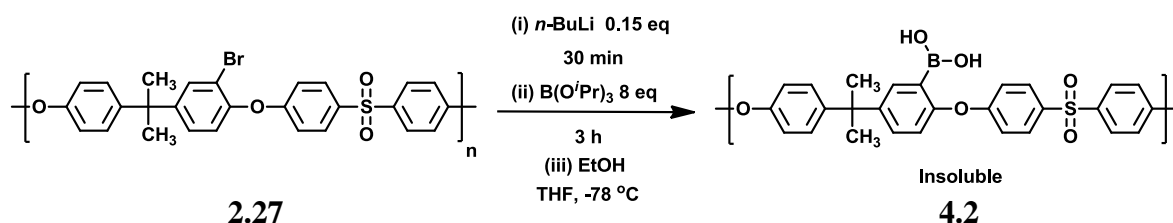
In order to test the first hypothesis, it was decided to reduce the equivalents of *n*-BuLi and borylating reagent, hoping that a less functionalised PSF may be soluble. B(OMe)<sub>3</sub> was also substituted with B(O<sup>*i*</sup>Pr)<sub>3</sub> owing to its availability as an anhydrous reagent in contrast to B(OMe)<sub>3</sub> which was supplied wet. Finally, assuming that the boronate esters would be more soluble than the boronic acids in organic solvents, the reaction was stopped by precipitation directly into MeOH, EtOH or hexane rather than quenching with aqueous acid in an attempt to prevent the conversion of the boronate esters into boronic acids. These changes however, did not produce a soluble polymer, even with only 0.15 equivalents of *n*-BuLi added (**Scheme 4.8**).





Scheme 4.8

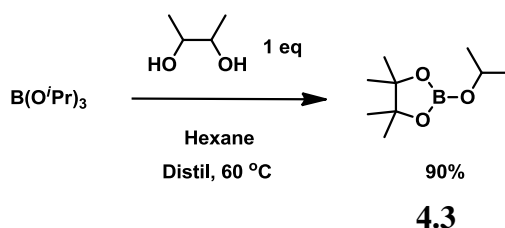
The same conditions were applied to brominated PSF **2.27** with similar results (Scheme 4.9).



Scheme 4.9

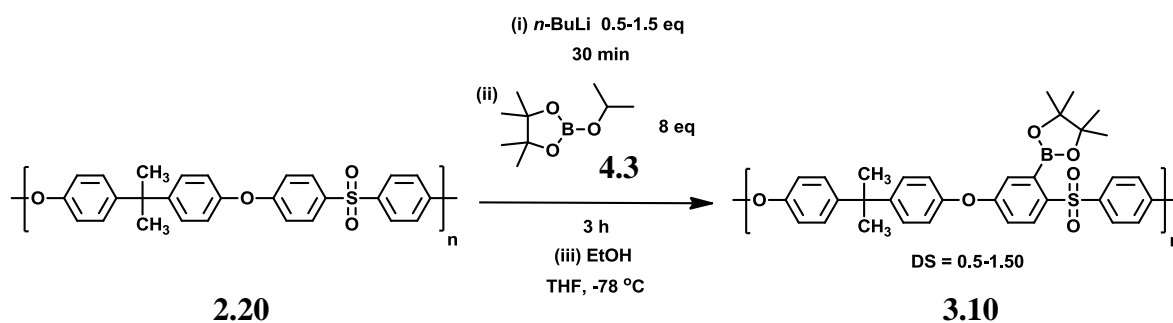
These results indicated that it was most likely a cross-linking issue rather than one of solubility. The obvious next step was to use a protected borylating reagent such that the generated borylated PSF was unable to cross-link. It was hypothesised that attaching a typical boron protecting group, such as pinacol, to B(O<sup>*i*</sup>Pr)<sub>3</sub> would give a species that would react with the lithiated PSF to afford a protected boronate ester functionalised PSF.

Isopropyl pinacol borate **4.3** was synthesised following a procedure by Andersen *et al.*<sup>13</sup> Equimolar amounts of B(O<sup>*i*</sup>Pr)<sub>3</sub> and pinacol were dissolved in hexane, whereupon they were heated at 60 °C. As the reaction progresses, isopropanol is produced and continuously azeotropically distilled with hexane out of the reaction mixture. Once the reaction is complete and all the solvent has been removed, the product is purified by distilling it into a fresh reaction vessel at 10 Torr to separate it from any unreacted pinacol (Scheme 4.10).



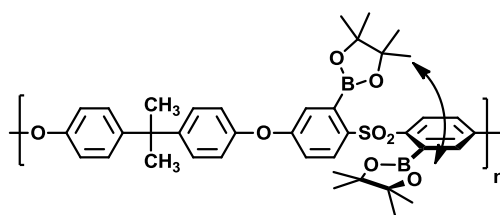
Scheme 4.10

Isopropyl pinacol borate **4.3** was added to lithiated PSF in the same manner as previous reactions to successfully afford the borylated PSF **3.10** substituted almost quantitatively with respect to the equivalents of *n*-BuLi used (Scheme 4.11).



Scheme 4.11

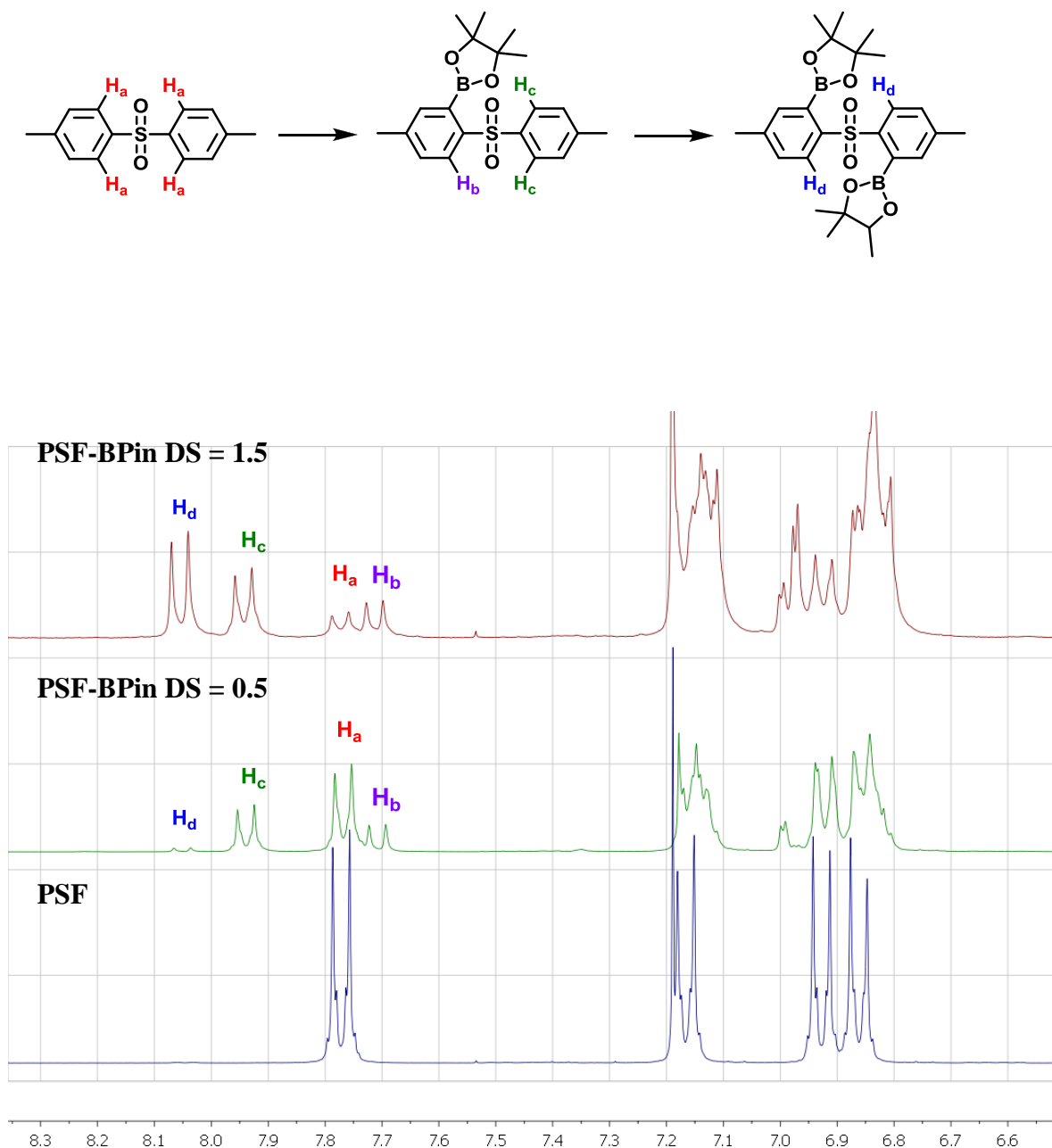
The resulting polymer **3.10** retained its solubility and thus the product could be quantified by  $^1\text{H}$  NMR in  $\text{CDCl}_3$ . It was envisaged that the overall yield could be easily determined by comparing the integration of the gem-dimethyl peak and the pinacol peak. However, there were some extra factors involved which complicated the analysis. In addition to the expected gem-dimethyl peak at  $\delta 1.61$  ppm and the pinacol peak at  $\delta 1.34$  ppm, there is a secondary pinacol signal between  $\delta 1.15$ - $1.21$  ppm, the strength of which increases in relation to an increase in DS. It is suspected that this signal comes from rotamer formation when two pinacol groups are attached to the same bisphenylsulfone unit (Scheme 4.12).



Scheme 4.12

Further complications arose upon inspection of the aromatic region. As the reaction progresses it is assumed that PSF is converted into monosubstituted borylated PSF and then into the diborylated species. Following this theory, the  $^1\text{H}$  NMR signal for  $\text{H}_a$  would be converted into  $\text{H}_b$  and  $\text{H}_c$  as the reaction reaches a DS of 1.0 (monosubstituted), and then the signals for  $\text{H}_b$  and  $\text{H}_c$  would be converted into  $\text{H}_d$  as the reaction nears a DS of 2.0 (disubstituted). This trend was not observed however, with signals for  $\text{H}_d$  being present at a DS of 0.5 and signals for  $\text{H}_a$  still remaining at DS of 1.5 (**Figure 4.1**).

The results indicate that the DS = 0.5 functionalised PSF, rather than being a mixture of mono and unsubstituted polymer, is in fact a statistical mixture of mono-, di- and unsubstituted polymer. Conversely, the DS = 1.5 functionalised PSF is a statistical mixture of mono, di and unsubstituted PSF, rather than simply a one to one mix of mono and disubstituted PSF. Whilst this effect is perhaps not unexpected, it needs to be taken into account when assessing PSF functionalised *via* lithiation.



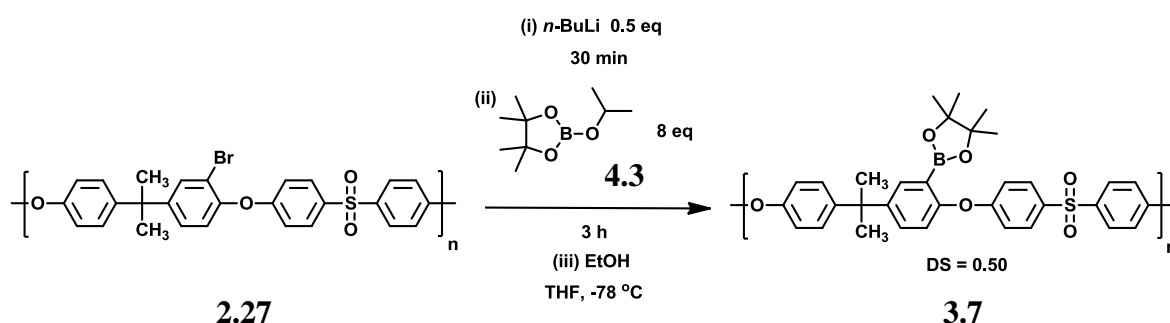
**Figure 4.1:** Overlay of 300 MHz  $^1\text{H}$  NMR spectra of PSF with DS = 0.5 and DS = 1.5 borylated PSF.

Another interesting feature of the  $^1\text{H}$  NMR is the apparent downfield shift of the  $\text{H}_c$  signal and upfield shift of the  $\text{H}_b$  signal in relation to  $\text{H}_a$ . The postulated explanation for this is that the oxygen of the sulfone moiety is interacting with the empty p-orbital on the adjacent boronate ester. On a monosubstituted sulfone unit, this electron withdrawing

effect causes electron density to be withdrawn from the non-borylated phenyl ring towards the borylated one, effectively deshielding the H<sub>c</sub> protons and shielding H<sub>b</sub>. On the disubstituted species, electron density is withdrawn from both rings, further deshielding H<sub>d</sub>.

As discussed in section 3.6, PSF **3.10** was investigated for its ability to undergo Suzuki couplings, although the research was unsuccessful. Also discussed in section 3.6 was the iridium catalysed C-H activation towards borylated PSF published by Jo *et al.*<sup>14</sup> This route however, is inferior to our own lithiation method due to a lack of control over regioselectivity as they form a mixture of *ortho*-ether and *ortho*-sulfone products.

Our method is able to control the regioselectivity and has the ability to selectively form either regioisomer. We were able to synthesise the *ortho*-ether product under the same conditions using brominated PSF **2.27**. The regioisomer **3.7** was successfully isolated with quantitative substitution with respect to the equivalents of *n*-BuLi used (**Scheme 4.13**).



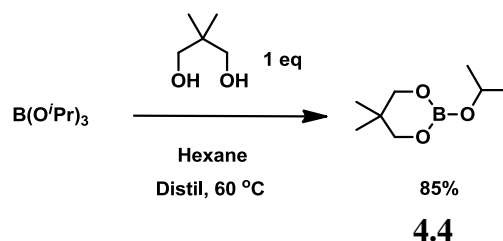
**Scheme 4.13**

Although halogen-lithium exchange is more favourable than *ortho*-sulfone deprotonation, small amounts of *ortho*-sulfone product do form. It should also be noted that if the amount of *n*-BuLi added was less than the level of bromination on the polymer, unreacted brominated sites would remain. In an attempt to obtain a product without these remaining bromine groups, a slight excess of *n*-BuLi was added in relation to the number of brominated sites. Upon quenching with a lower amount of borylating reagent any remaining lithiated sites were quenched by the hydrolytic workup to regenerate the

aromatic hydrogens. This however, gave poor yields, presumably owing to the excess lithiated sites interfering with the borylation process.

It was intended that these directly borylated polymers could afford simple separation processes, however the strength of the pinacol protecting group posed a potential problem. Pinacol forms a very stable boronate ester with boronic acids that tends to require strong conditions to remove; either acid hydrolysis or reaction with  $\text{KHF}_2$  followed by hydrolytic work up. In order to access the free boronic acid it was intended that the deprotection process would happen heterogeneously, after being spun into a hollow fibre. This however, might not be suitable, since the deprotection conditions could potentially cause adverse effects on the fibre. Therefore, having achieved a suitable borylation method, the use of a more labile protecting group was investigated.

In comparison with pinacol, neopentyl glycol requires only mild conditions to deprotect and thus was chosen to replace pinacol. Isopropyl neopentyl glycol boronate **4.4** was synthesised in the same manner as the pinacol variant (**Scheme 4.14**).

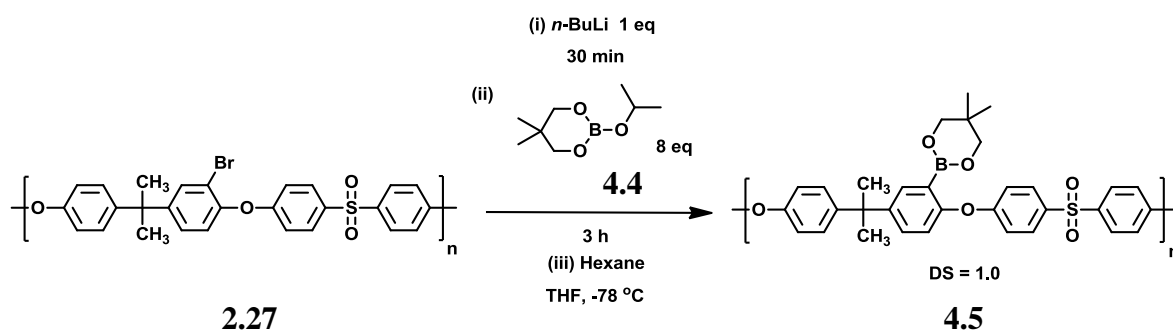


**Scheme 4.14**

Brominated PSF **2.27** was reacted with the neopentyl borylating reagent **4.4** as it was speculated that the proximity of the sulfone moiety at the *ortho*-sulfone position may increase the lability of the protecting group to an undesirable level. The *ortho*-ether position is also less sterically hindered, which may favour any separation attempted by the final fibres.

The procedure was modified slightly from the previous method. Normally the reaction is quenched by precipitation into EtOH, followed by a lengthy process of successive washing

and filtrations. However, the stability of the neopentyl boronate ester to this process was suspect and thus the precipitation and washings were undertaken with anhydrous hexane. Neopentyl glycol boronate ester functionalised PSF **4.5** was synthesised quantitatively (Scheme 4.15).

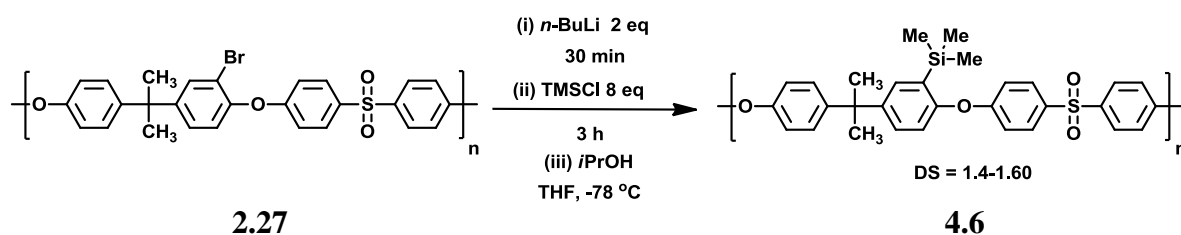


Scheme 4.15

#### 4.4 Borodesilylation

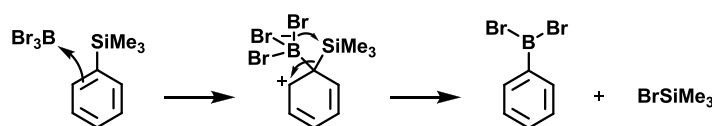
Aryllithium and aryl Grignard reagents both undergo reactions with silylhalide reagents such as TMSCl, to produce aryl silanes. Although aryl silanes are not commonly used as reactive intermediates, they are able to undergo a range of substitution reactions including nitration, sulfonation, halogenation and acetylation.<sup>15-17</sup>

Following the procedure proposed by Guiver *et al.*<sup>7</sup> shown in Scheme 4.16, silylated PSF **4.6** was synthesised at near quantitative yields from brominated PSF **2.27**.



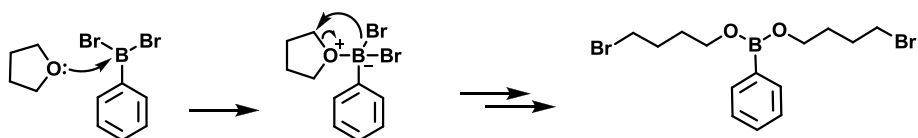
Scheme 4.16

Arylsilanes can also undergo borodesilylation reactions when exposed to boron trihalides such as  $\text{BBr}_3$ ; a classical method for the preparation of boronic acids. The reaction produces a dibromoboron species (**Scheme 4.17**) which is not isolable, but can be hydrolysed to produce boronic acids or esters.



**Scheme 4.17**

Qin *et al.*<sup>18</sup> used the borodesilylation methodology to create boronic acid functionalised polystyrene. Interestingly they did not isolate the boronic acid *via* hydrolytic work up. Instead, they reacted the produced dibromoboryl species with THF to generate bisbromobutoxyboryl functionalised polystyrene (**Scheme 4.18**).



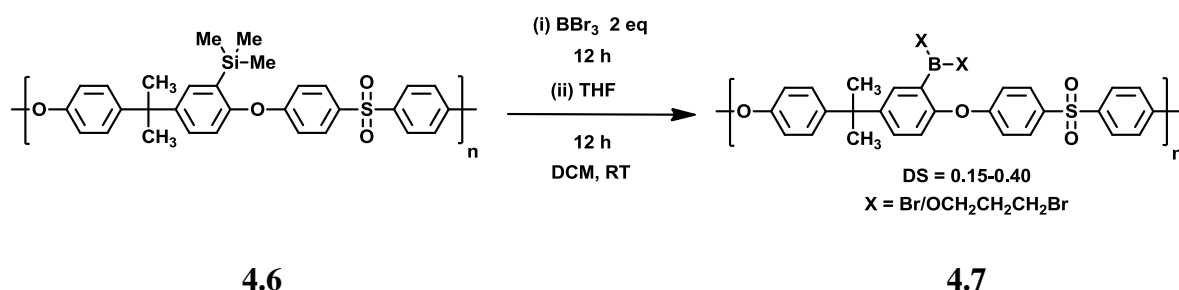
**Scheme 4.18**

Therefore it was plausible that the borodesilylation could provide an alternate route to boron appended PSF and the bisbromobutoxy boronic ester might also provide a soluble polymer possessing functionality without requiring deprotection, unlike the previous methods.

To a solution of silylated PSF **4.6** dissolved in anhydrous DCM was added 2 equivalents of  $\text{BBr}_3$  and the reaction stirred for 12 hours, after which time the reaction was quenched by



addition of a large excess of THF. The resultant PSF was desilylated by 15-40%, indicating a DS of 0.15-0.40 of borylated polymer (**Scheme 4.19**).



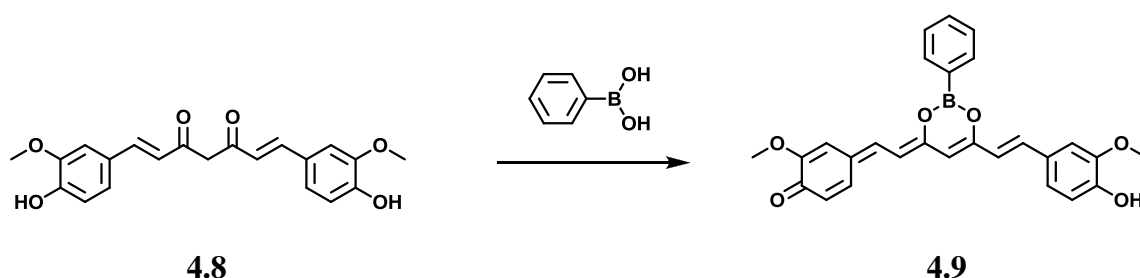
**Scheme 4.19**

The reaction was quantified by  $^1\text{H}$  NMR, by a decrease in the *ortho*-sulfone and *ortho*-ether TMS peaks at  $\delta$ 0.34 ppm and  $\delta$ 0.18 ppm respectively, as well as a decrease in the aromatic peak at  $\delta$ 6.75 ppm of the proton *meta* to the TMS. The integration of the butyl peaks however did not correspond to loss of the TMS peaks, indicating that the boronate ester is not readily forming or potentially that the starting material is being desilylated by a different pathway.

The  $^{11}\text{B}$  spectra also failed to give a peak for either a boronic acid or a boronate ester. Normally this would indicate that boron is not present in the compound and that the reaction had failed, however the previously synthesised boron containing PSF compounds **3.7**, **3.10**, and **4.5** often failed to give signals in  $^{11}\text{B}$  NMR even though the attached pinacol or neopentyl groups were clearly visible in their respective  $^1\text{H}$  and  $^{13}\text{C}$  spectra. This is perhaps not unsurprising as the combination of a polymeric species and a quadrupolar nucleus such as boron, both of which lead to broad resonances, might together give a resonance that is broadened so much it is indistinguishable from the baseline in the  $^{11}\text{B}$  spectrum. Normally, the breadth of resonances from quadrupole nuclei get significantly larger as the size of the molecule gets bigger, and this can often lead to a signal too broad to be observed.<sup>19</sup>

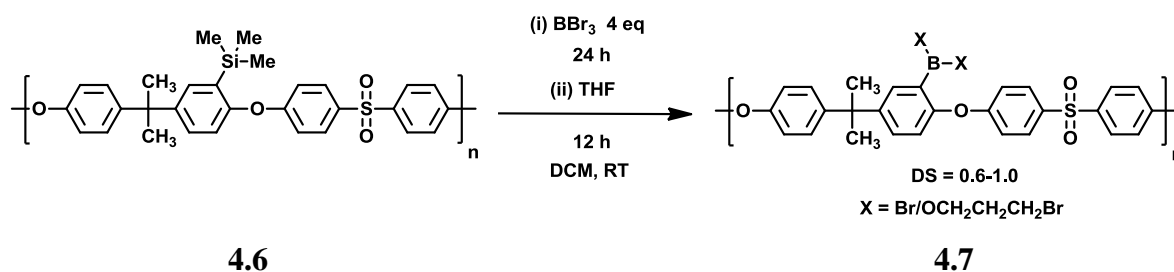
Therefore in order to determine whether boron is present within the polymer or if an alternative desilylation pathway is responsible for the loss of the TMS signal, we used a boron indicating stain.

Developed within our group<sup>20</sup> it was found that an acidic mixture of curcumin **4.8** and ethanol would form a brightly coloured orange complex with boronic acids which when used as a TLC stain would selectively indicate whether boronic acids, esters or halides were present within a sample (**Scheme 4.20**).



**Scheme 4.20**

As the produced polymer indicated positive for boron content by this method, it was assumed that the initial borylation step was successful, although in a low yield. The reaction conditions were changed to include an increased reaction time and a greater excess of  $\text{BBr}_3$ , leading to a greater degree of desilylation (**Scheme 4.21**).



**Scheme 4.21**

Whilst this is a great improvement on the previous attempt, it is still somewhat surprising that such a great excess of highly reactive  $\text{BBr}_3$  failed to take the reaction to completion. A range of quenching agents were also tried. Pinacol and neopentyl glycol were added directly to the reaction in an attempt to give protected boronate esters. Unfortunately this again failed to generate the desired compound in yields equivalent to the loss of the TMS peaks, indicating that the esterification reaction requires stronger conditions than attempted, potentially requiring reflux temperatures.

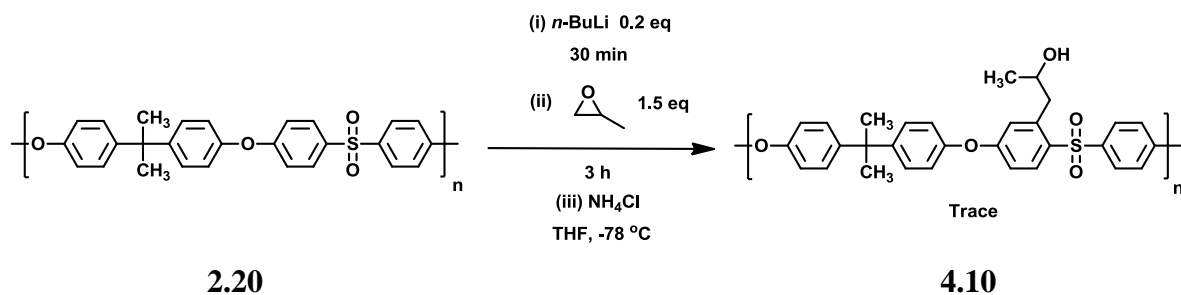
At this point it was decided that this route was inferior to the direct borylation procedure. Concerns over the large amount of highly poisonous  $\text{BBr}_3$  used as well as the potential for it to cleave the polymer chains when used under harsher conditions led us to discontinue the optimisation of the reaction, especially considering a relatively mild route to a chain functionalised boronic acid had already been developed.

#### 4.5 Epoxide Ring Opening

As discussed previously in section 3.3, an azide functionalised polymer would allow modular functionalisation *via* “click” chemistry and so is a desirable functionality to install. Guiver *et al.*<sup>9</sup> synthesised main chain azide functionalised PSF from the reaction of lithiated PSF with tosyl azide, however there were safety concerns regarding the explosive nature of aromatic and polymeric azides and therefore this route was not undertaken by us.<sup>21,22</sup>

In section 3.4 we discussed our attempts at Lewis acid catalysed epoxide ring openings to achieve primary alcohol functionalised PSF, with the ability to easily convert the alcohol into an azide group. These reactions failed and it was postulated that an organolithium initiated epoxide ring opening reaction might proceed under milder conditions to give a higher yield.

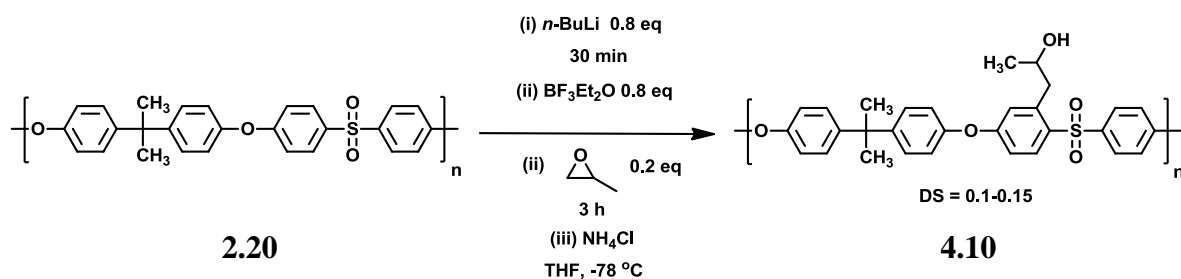
Initially excess propylene oxide was added to lithiated PSF followed by an acidic work up in the hope of generating the desired primary alcohol **4.10**. It was suspected that a polymer with a high degree of alcohol groups may prove insoluble so lithiation was limited to a DS of 0.20 for the first reaction (**Scheme 4.22**).



Scheme 4.22

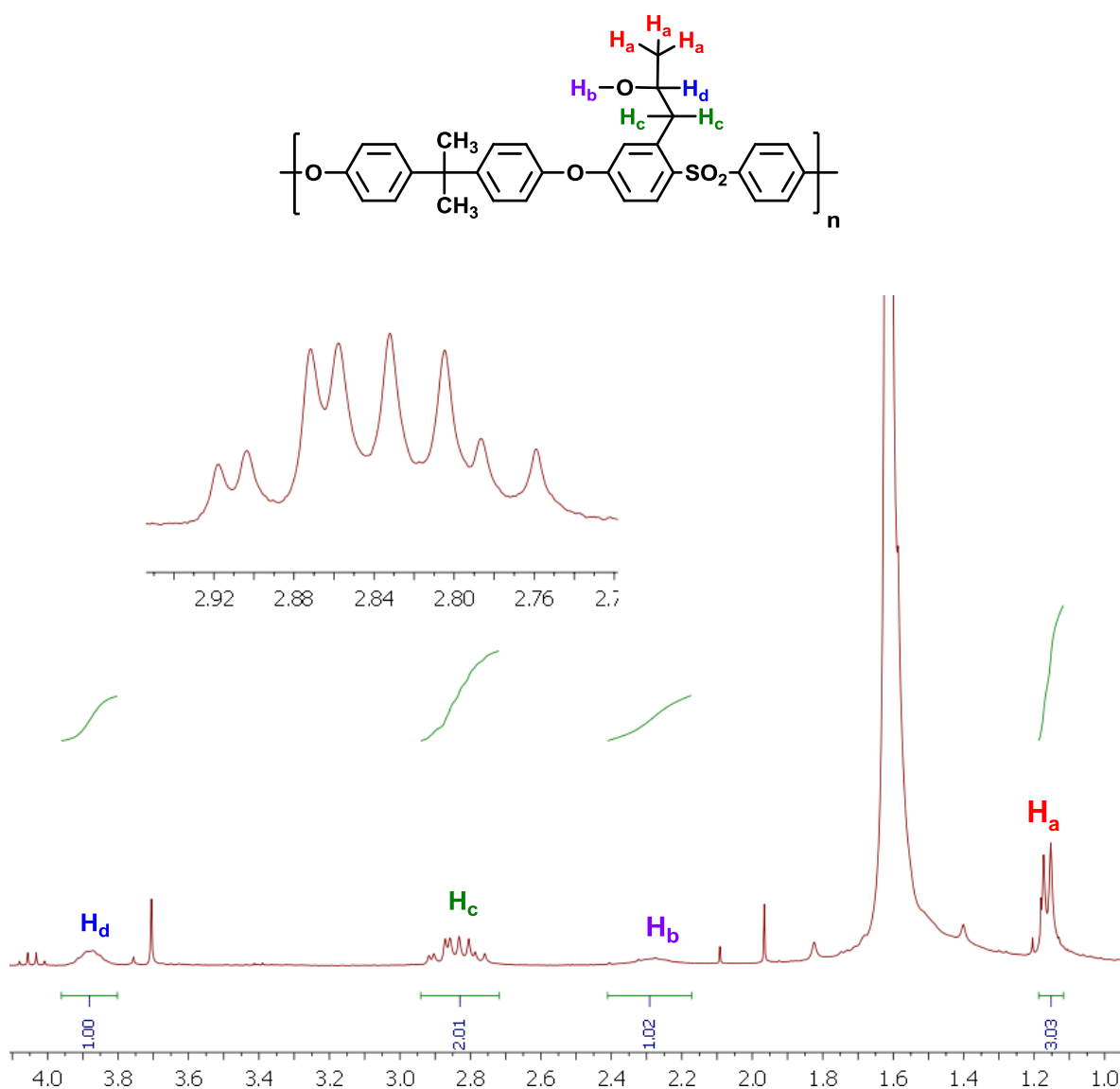
This method proved unsuitable, giving a small amount of mixed product; a mix of isomers and potentially small amounts of cross-linked product. Fortunately, literature precedence existed showing that  $\text{BF}_3\cdot\text{Et}_2\text{O}$  is surprisingly stable in the presence of organolithium reagents in THF and a dual organolithium/Lewis acid approach to epoxide ring opening provides good yields.<sup>23-26</sup>

As with the previous attempt, we initially desired a low degree of functionalisation, so aimed for a DS of 0.20. Using conditions provided by Goujon *et al.*<sup>26</sup> 0.8 equivalents of  $n\text{-BuLi}$  and  $\text{BF}_3\cdot\text{Et}_2\text{O}$  were added to a solution of PSF in anhydrous THF and cooled to  $-78^\circ\text{C}$ . Subsequently 0.2 equivalents of propylene oxide, followed by an excess of  $\text{NH}_4\text{Cl}$  were added. The reaction gave a DS of 0.10-0.15 ring opened product **4.10** which retained its solubility (**Scheme 4.23**).



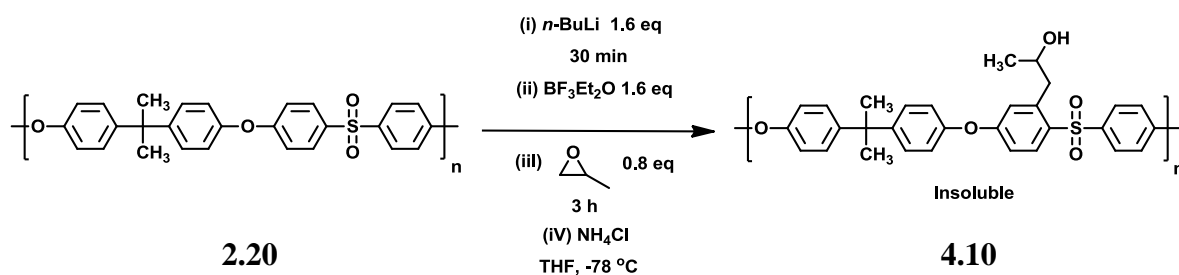
Scheme 4.23

Due to the low level of functionalization, obtaining an accurate DS *via*  $^1\text{H}$  NMR was difficult due to the small size of the peaks in comparison to the polymer backbone, hence the range given. The desired product was achieved to at least a DS of 0.10 which is respectable considering only 0.2 equivalents of propylene oxide were added. Whilst minor amounts of the propan-1-ol product is formed, the vast majority is the propan-2-ol product, apparent by the distinct pair of doublet of doublets at  $\delta 2.83$  ppm corresponding to  $\text{H}_c$ . This complex multiplet results from the use of racemic propylene oxide causing a diastereotopic centre to form (**Figure 4.2**).



**Figure 4.2:** 300 MHz  $^1\text{H}$  NMR of epoxide ring opening product.

As the low equivalent functionalisation was successful, the reaction was repeated with 0.8 equivalents of propylene oxide in the hope that PSF functionalized to a DS of 0.5-0.60 would be produced, as this is the minimum level of functionalization required to produce a suitable membrane. Unfortunately an insoluble product formed (**Scheme 4.24**).



**Scheme 4.24**

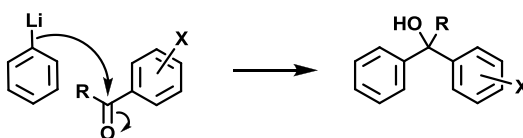
As feared, when the level of functionalisation with the hydrophilic alcohol becomes too high the produced polymer loses all solubility. As such, the epoxide ring opening methodology whilst useful for making polymers at low levels of substitution is not suitable for our needs as the polymers of the desired level of functionalisation are insoluble in useful solvents.

From this it was clear that functional groups with a low level of hydrophilicity are necessary to maintain the polymer's solubility.

#### 4.6 Reaction with Aldehydes

The focus of our research thus far has been to functionalise PSF with a reactive group which could then be further functionalised with a range of compounds to give the desired functional polymer. Rather than trying to functionalise the polymer in this step-wise manner, an alternative route could be to install the whole unit of tether, linker and receptor in one reaction.

A standard reaction of lithiated compounds is that with aldehydes and ketones, which results in the formation of secondary or tertiary alcohols. It is envisaged that this methodology could be used to attach functionality to the PSF whilst generating a semi-flexible linker in the process (**Scheme 4.25**).



**Scheme 4.25**

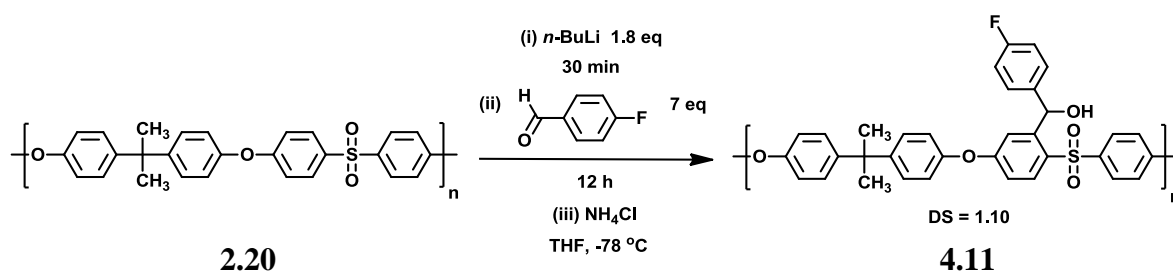
Yamamoto *et al.*<sup>27</sup> successfully reacted different formyl boronate esters with a range of complex lithiated heterocycles showing that they are compatible with this chemistry. This suggested that we could produce a fully functionalised boronic acid appended PSF simply by reacting the lithiated polymer with a formyl boronate ester.

The methodology has also been applied to PSF by Kerres *et al.*<sup>28</sup> who reacted lithiated PSF with a series of formyl, ketone and ethylester derivatives of some pyridyl and diethylaminobenzene compounds to give a polymer functionalised by basic groups. They used a large excess of *n*-BuLi and the relevant reactant in order to try and minimise the potential cross-linking reaction. They achieved a polymer with a degree of substitution between 1 and 3.5.

Considering boronic acids are relatively expensive reagents, we initially investigated this reaction using a non-boronic acid containing aldehyde. Specifically we chose 4-formylfluorobenzene as it was readily available in house and because the fluorine could act as an analytical tag, causing the product to be <sup>19</sup>F NMR active.

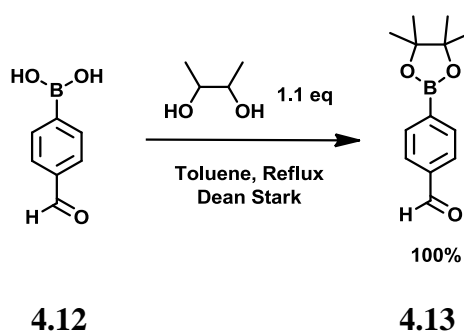
Following the conditions proposed by Kerres *et al.*,<sup>28</sup> we used 4 equivalents of *n*-BuLi followed by an excess of the aldehyde to generate the polymer **4.11** with a DS of 1.1 (**Scheme 4.26**). The yield is clearly determinable by integrating the distinct singlet at

$\delta 6.40$  ppm in the  $^1\text{H}$  NMR which corresponds to the  $\text{CH-OH}$  signal which has been shifted downfield by the adjacent sulfone moiety.



Scheme 4.26

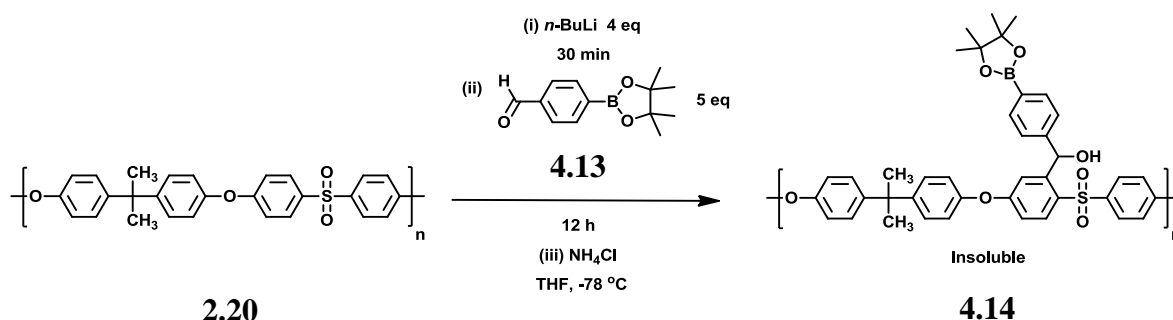
Following the success of this functionalisation we conducted the reaction with our desired boronate containing aldehyde. To incorporate the boronate and linker we chose to use pinacol protected 4-formylphenylboronic acid **4.13**. This was easily synthesised from the corresponding, commercially available boronic acid by Dean Stark reflux in toluene (Scheme 4.27).



Scheme 4.27

Surprisingly, employing aldehyde **4.13** under the same conditions as Scheme 4.26 produced an insoluble product (Scheme 4.28).



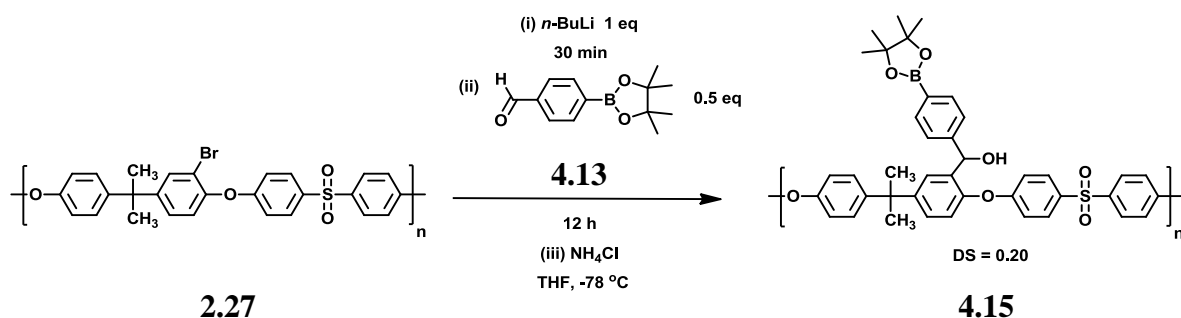


Scheme 4.28

This was unexpected as pinacol is a good protecting group which forms non-polar boronic esters, therefore the boronic ester should not interfere with the solubility and as such it should have been equivalent to the fluorinated PSF **4.11** which was chloroform soluble. The polymers produced by Kerres *et al.* were generally DMSO soluble, but our polymer still gelled when exposed to DMSO, remaining insoluble. It was however, soluble in  $\text{D}_2\text{SO}_4$  which whilst not producing suitable  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra gave a strong signal at  $\delta$ -8.76 ppm in the  $^{11}\text{B}$  spectra, potentially from an  $[\text{ArB}(\text{OSO}_3\text{H})_3]^-$  species.<sup>29</sup> This at least indicated boron was present on the polymer.

It was hypothesised that potential interactions between the boronate ester and neighboring alcohol groups could be causing the lack of solubility *via* electrostatic cross-linking. Alternatively, the reaction could be proceeding to a higher yield than the fluorinated equivalent to the point where the polymer has lost solubility due to the large amount of hydrophilic alcohol groups present. In order to investigate this we changed conditions in line with our previous work, to much lower equivalents of aldehyde and  $n\text{-BuLi}$ . We also switched to using brominated PSF to avoid any issues potentially caused by the sulfone group.

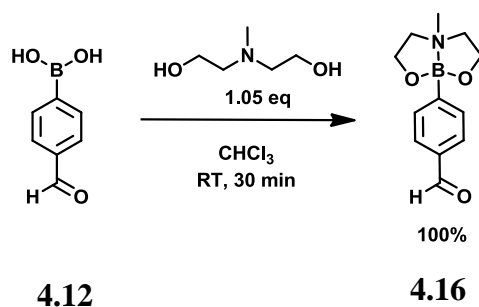
Using brominated PSF DS = 0.80 with 1 equivalent of  $n\text{-BuLi}$  and 0.5 equivalents aldehyde we achieved a soluble polymer, *ortho*-ether functionalised to 20% (Scheme 4.29). Again the yield was determined by the integration of the  $\text{CH-OH}$   $^1\text{H}$  NMR peak at  $\delta$ 5.90 ppm, which is shifted upfield compared to the *ortho*-sulfone equivalent.



Scheme 4.29

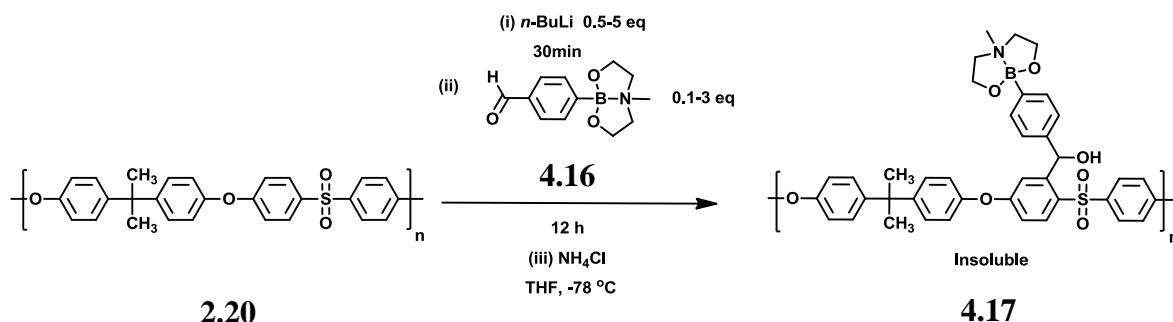
Attempts to improve the DS above 0.2 failed as the polymer quickly became insoluble. This indicates that the boronic ester is probably interfering with the solubility. In order to address this we replaced pinacol with *N*-methyldiethanolamine, a tridentate protecting group, in the hope that it would create a soluble polymer by blocking potential interactions between the alcohol groups and boron's empty p-orbital.

*N*-methyldiethanolamine was stirred with 4-formylphenylboronic acid **4.12** in  $\text{CHCl}_3$  for 30 minutes at room temperature to synthesise the protected boronate **4.16** in quantitative yield (Scheme 4.30).



Scheme 4.30

Unfortunately, employing this new aldehyde achieved no further improvement. The polymers produced were insoluble in  $\text{CHCl}_3$  and gelled in DMSO, even when low equivalents of reactants were used (**Scheme 4.31**).



**Scheme 4.31**

It is possible that the tridentate boronate ester, whilst preventing some of the issues associated with the pinacol ester, causes different solubility problems due to its charged nature.

Despite initially affording promising results, the reaction of lithiated PSF with aldehydes proved to be unsuitable due to the inability to produce soluble boronic acid functionalised polymers. Even when successful, the methodology required a large excess of reagents, which is not only undesirable for large scale synthesis, but is contrary to standard organolithium reactions, suggesting the reaction is a difficult one.

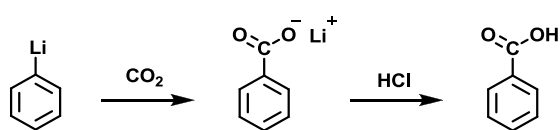
In order to try and avoid the solubility problems we faced, it was decided to revert back to modifying the polymer with groups for further functionalisation rather than adding the whole unit in one go, so as to afford better control over the polymer's solution properties.

## 4.7 Carboxylation

Another commonly used reaction of aryllithium compounds is that with dry ice ( $\text{CO}_2$ ) to yield a carboxylated product. This is a desirable functionalisation to achieve, since

carboxylic acids readily undergo peptide coupling and acid chloride mediated reactions to form amides and esters.

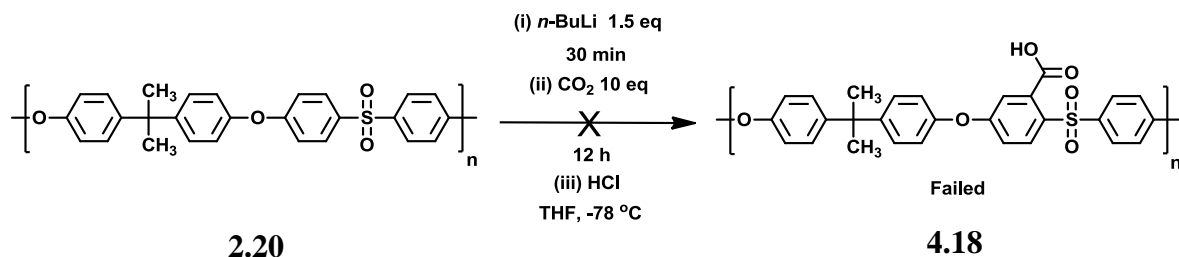
Guiver *et al.*<sup>6</sup> investigated the *n*-BuLi mediated carboxylation of polysulfone and found the reaction to be superior to the equivalent polystyrene reactions. The reaction on polymers is not as simple as it initially appears; it proceeds *via* a lithium carboxylate salt which creates an incredibly viscous solution which requires conversion to the desired carboxylic acid by acidic workup (**Scheme 4.32**).



**Scheme 4.32**

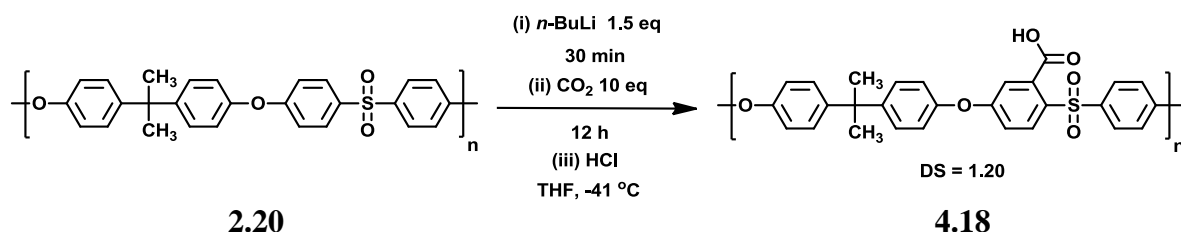
In order to avoid this unwanted viscosity, which would result in poor mixing of the reaction and therefore lower yields, they increased the reaction temperature to -50 °C from the usual -78 °C and used a large amount of solvent to give a more dilute solution.

In comparison to the large 1 lb blocks of CO<sub>2</sub> used by Guiver *et al.* we had access to small CO<sub>2</sub> pellets, which led us to believe that less vigorous stirring and a lower excess would be required. Also, we initially attempted the reaction at -78 °C due to the ease of use of CO<sub>2</sub>/acetone cooling baths. After lithiating the polymer in the standard fashion, the CO<sub>2</sub> pellets were quickly added to the mixture through a stream of N<sub>2</sub> in order to minimise moisture condensation. The resultant solution became extremely viscous, to the point where stirring ceased even with a very large magnetic stirrer, causing the reaction to fail (**Scheme 4.33**).



Scheme 4.33

Evidently the low temperature was not suitable and the reaction was repeated at -41 °C using a CO<sub>2</sub>/acetonitrile cooling bath. Unfortunately this also resulted in a mixture which was too viscous to stir with a magnetic stirrer. On top of the precautions already discussed, Guiver *et al.* addressed this issue by mixing the solution vigorously with a metal spatula. In order to recreate this effect with the glassware available to us, upon addition of CO<sub>2</sub> the round bottom flask containing the solution was rapidly shaken in a circular motion whilst submerged in the cooling bath. This resulted in good mixing, allowing the reaction to proceed to completion to produce carboxylated PSF **4.18** (Scheme 4.34).



Scheme 4.34

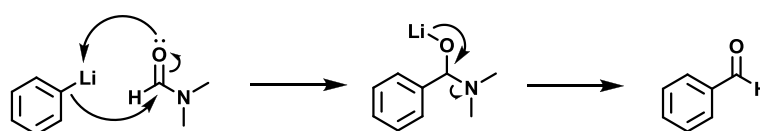
The polymer was functionalised with a DS of 1.2 and although insoluble in CHCl<sub>3</sub> it was soluble in DMSO allowing quantification by <sup>1</sup>H NMR. The multiplets between δ7.80-8.10 ppm belong to the *ortho*-sulfone aromatic protons and the difference in integration of these peaks versus the integration of the equivalent starting material peak is equivalent to the amount of functionalisation achieved.

Whilst this process was successful on a small 2.5 g scale reaction, the need to physically agitate the flask is potentially unsafe, especially due to the reactive nature of *n*-BuLi. This risk increases exponentially as the reaction is scaled up, with larger reaction vessels entirely unsuited to this process. The obvious solution is to use a mechanical overhead stirrer, equipped with an adapter for air sensitive chemistry, to achieve a high level of mixing. This equipment was unavailable to us so whilst the reaction is a successful route to a functionalised PSF, it could not be used to produce it on the scale that was necessary and thus this line of experimentation was concluded.

#### 4.8 Formylation

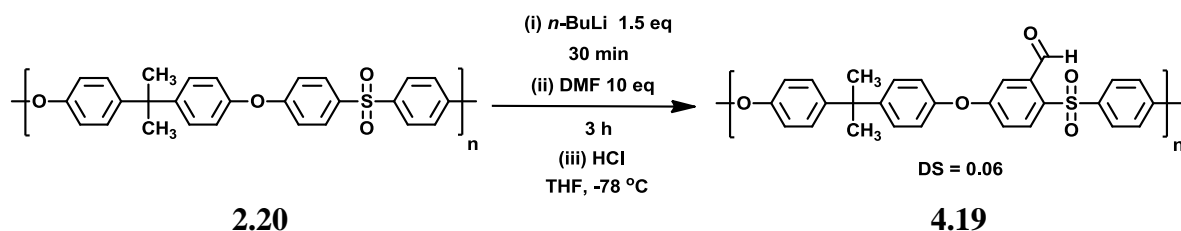
As discussed in section 3.5, the ability to generate aldehyde functionalised PSF is highly desirable as aldehydes are generally non-reactive enough to allow clean functionalisation, but have the ability to readily react when further functionalisation is required. Attempts to achieve this *via* electrophilic aromatic substitution failed, so an organolithium route was investigated.

The most common route is the reaction of a lithiated species with DMF, a reaction widely used to formylate complex heterocycles<sup>30</sup> and alkynes<sup>31</sup> (**Scheme 4.35**).



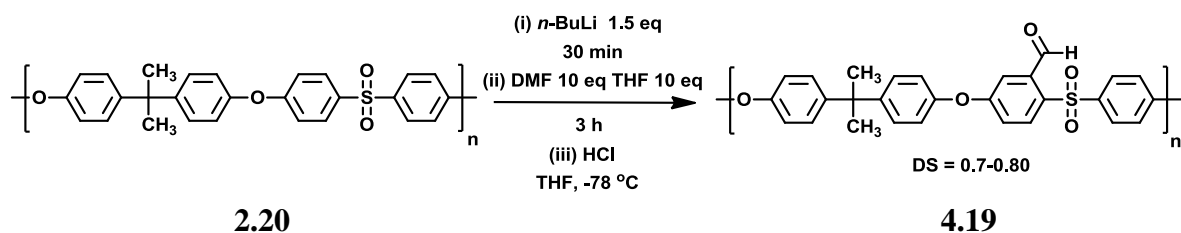
**Scheme 4.35**

Owing to the perceived ease of this reaction, the formylation of PSF was attempted using the standard conditions of rapid addition of excess DMF to lithiated PSF stirred at  $-78^{\circ}\text{C}$  in THF (**Scheme 4.36**). Surprisingly, the reaction only produced a minimal amount of formylated PSF **4.19**, suggesting that the reaction was not as simple as first suspected.



Scheme 4.36

It was noted that upon addition of DMF the solution became extremely viscous and the polymer temporarily precipitated. This was most likely owing to PSF having limited solubility in DMF which has a freezing point of  $-60\text{ }^\circ\text{C}$ . In order to address this situation we experimented with dissolving the DMF in THF and cooling the mixture prior to injection into the reaction. We also increased the amount of solvent in the reaction mixture and varied the equivalents of *n*-BuLi to obtain optimum conditions. It was found that a DS of up to 0.8 was obtainable when a large excess of cooled DMF dissolved in THF was added to PSF lithiated by 1.5 equivalents of *n*-BuLi (Scheme 4.37).



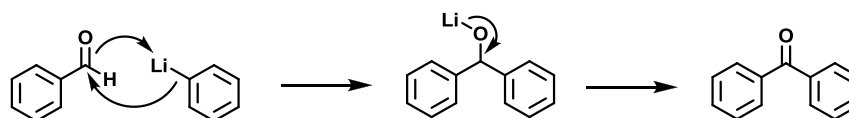
Scheme 4.37

When looking at the  $^1\text{H}$  NMR of formylated PSF **4.19** the expected signal from the aldehyde peak appeared as two separate singlets. The peak at  $\delta 10.77$  ppm is from the monosubstituted product and the second peak at  $\delta 10.56$  ppm is from the disubstituted product. Interestingly there was a 3:1 ratio of monosubstituted monomer units and

disubstituted monomer units. The high proportion of disubstitution indicates that the substituted bisulfone unit is more reactive than the unsubstituted bisulfone unit.

The maximum yield achieved was acceptable for our needs, however, the reaction was unpredictable and we failed to get consistently reproducible results over different batches. Also, when a higher degree of substitution was attempted by increasing the equivalents of *n*-BuLi an insoluble product was isolated. This suggested that on top of the earlier issues surrounding the dissolution of DMF, there was potentially an undesired side reaction occurring.

Guiver *et al.*<sup>5</sup> investigated the formylation of PSF and came to a similar conclusion regarding the difficulty of formylating PSF. They suggested that the proximity of the electron withdrawing sulfone moiety to the newly formed aldehyde group caused it be highly reactive, leading to a competing cross-linking mechanism (**Scheme 4.38**).



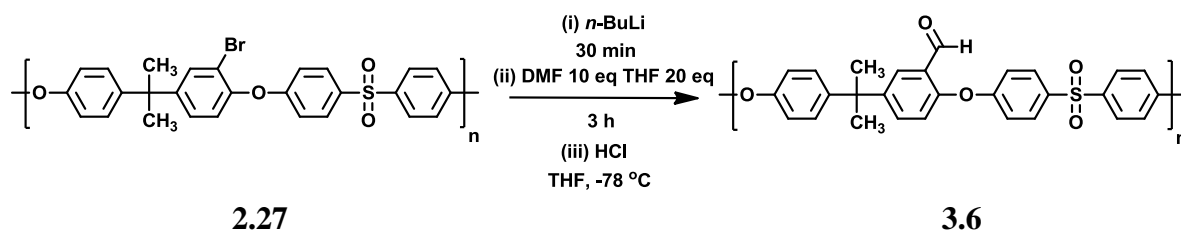
**Scheme 4.38**

They eventually developed a fairly complex method for producing the desired formylated PSF reproducibly to high degrees of functionalisation. This required a very dilute 4% solution of PSF, a reaction temperature of -60 °C, rising to -50 °C upon injection of the DMF/THF mixture and larger than usual equivalents of *n*-BuLi. They also applied this methodology to achieve *ortho*-ether formylated PSF from the brominated starting material.

Considering the issues faced in this reaction, which stem from the proximity of the sulfone, we believed that the *ortho*-ether reaction would proceed readily under standard conditions, not requiring the dilution or temperature changes employed by Guiver *et al.* Gratifyingly this assumption was correct and we were able to generate *ortho*-ether formylated PSF **3.6** in excellent yield from brominated PSF **2.27**. Impressively, the yield can be precisely



controlled by the stoichiometry of *n*-BuLi to furnish formylated PSF in any desired yield. Conveniently, the reaction was easily scaled up to 15 g with no issues (**Table 4.1**).

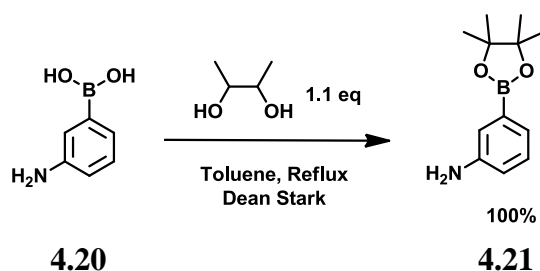


| <i>n</i> -BuLi eq | DS  |
|-------------------|-----|
| 0.8               | 0.6 |
| 1                 | 0.8 |
| 2                 | 1.8 |

**Table 4.1:** Relationship between amount of *n*-BuLi added and subsequent DS of produced formylated PSF.

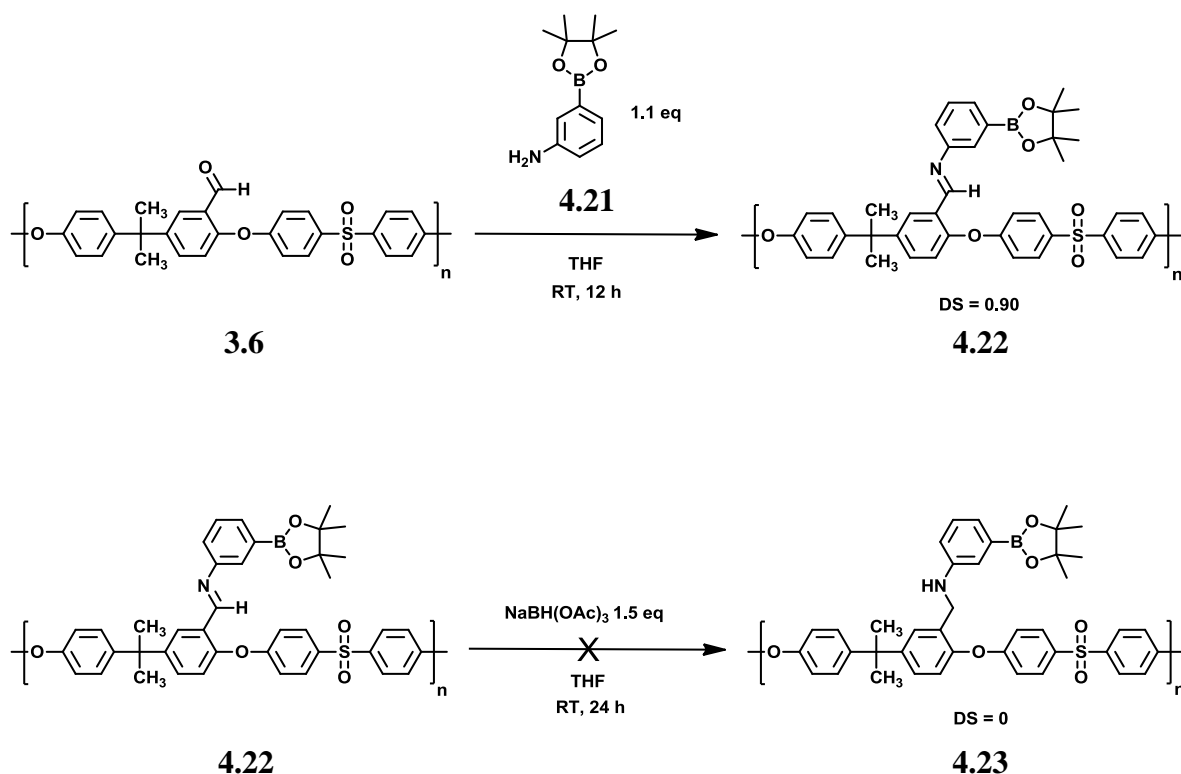
In the *ortho*-ether formylation, there was an increase in viscosity upon addition of the DMF/THF mixture, however the reaction fortunately still proceeded to completion with no ill effects. Examination of the  $^1\text{H}$  NMR spectra indicates there is no splitting of the aldehyde peak as there was with the *ortho*-sulfone disubstituted product with a singlet appearing at  $\delta 10.30$  ppm. There is however, a minor amount of *ortho*-sulfone product present, as denoted by the peak at  $\delta 10.77$  ppm.

Having isolated a relatively large amount of highly functionalised PSF from a robust procedure, we proceeded to experiment with the addition of a boronic acid unit. The most common reaction with aldehydes is reductive amination; the reaction of an aldehyde with a primary amine to form an imine which is subsequently reduced to generate the target secondary amine. As such, we synthesised pinacol protected 3-aminophenylboronic acid **4.21** under identical conditions to the previous protection reactions (**Scheme 4.39**).



Scheme 4.39

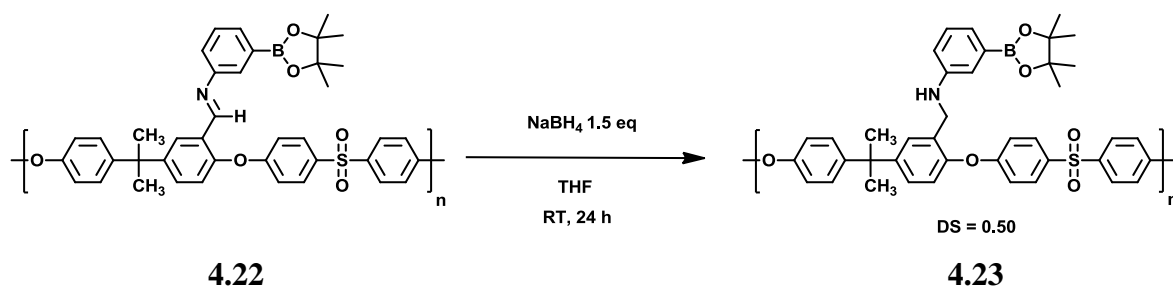
Initially we attempted the reductive amination of **3.6** using  $\text{NaBH}(\text{OAc})_3$ , a mild reducing agent capable of reducing imines, but not the starting aldehyde, therefore any unreacted aldehydes will remain unaffected. Addition of a slight excess of amine **4.21** to formylated PSF **3.6** in THF was followed by stirring for 12 hours to form the imine. A large excess of  $\text{NaBH}(\text{OAc})_3$  was added and the reaction stirred for a further 24 hours. The  $^1\text{H}$  NMR of the polymer produced showed a large pinacol peak from the added boronate ester suggesting the reaction was successful, however the expected  $\text{CH}_2\text{-NH}$  signal between  $\delta 3\text{-}5$  ppm was entirely absent. This suggests that the reduction step of the reaction failed, a hypothesis supported by the peak at  $\delta 8.7$  ppm from the intermediate imine proton. Thus the isolated product is most likely the imine **4.22** (Scheme 4.40). As with some previous polymers the  $^{11}\text{B}$  spectra afforded no signal, however the combination of the strong pinacol signal in the  $^1\text{H}$  spectra and the positive test with the aforementioned curcumin solution is strong evidence for its inclusion onto the PSF.



Scheme 4.40

Evidently the conditions employed were too mild to effect the desired transformation. Abdel-Magid *et al.*<sup>32</sup> discussed in great detail various ways to optimise a wide range of reductive aminations using  $\text{NaBH}(\text{OAc})_3$ , suggesting that DCE was a superior solvent to THF and that an equimolar amount of AcOH added to the reaction mixture improved the speed by catalysing the intermediate imminium ion formation. However, since the imine is readily formed it seemed simpler to use a strong reducing agent such as  $\text{NaBH}_4$  rather than attempt to optimise the  $\text{NaBH}(\text{OAc})_3$  reaction.  $\text{NaBH}_4$  is a much stronger reducing agent and as such will convert any unreacted aldehydes to primary alcohols.

Using the same conditions as **Scheme 4.40** with  $\text{NaBH}_4$  resulted in a 50% conversion of the imine **4.22** into the desired amine **4.23**, a much improved result over  $\text{NaBH}(\text{OAc})_3$ . Evidently full conversion would require increasing the equivalents of reducing agent and potentially a longer reaction time in order to push the reaction to completion (**Scheme 4.41**).



Scheme 4.41

At the outset of our research we aimed to be able to functionalise PSF quickly, cleanly, to high yields and on a large scale. The *n*-BuLi formylation reaction has clearly successfully achieved these objectives. The formylated PSF can readily react with amines to incorporate the desired boronic acid functionality connected by a flexible linker. There is also the potential for varying the amine used to easily generate a range of differently functionalised polymers. PSF **4.23** is an ideal polymer for taking forward to hollow fibre synthesis and warrants further research.

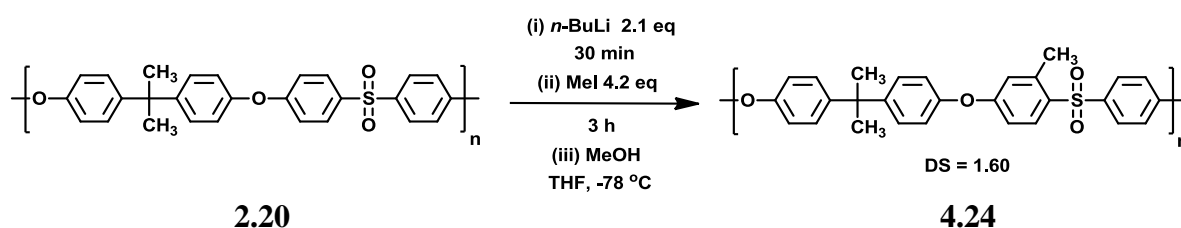
#### 4.9 Bromomethylation

Throughout our research we have investigated functionalising PSF with a wide range of functional groups with varying success. Out of all the transformations investigated, chloromethylation was perhaps the most desirable as it produces a group reactive enough to undergo a large range of simple transformations yet one which should not affect the solubility of the produced polymer. Unfortunately attempts to facilitate chloromethylation thus far have proved unsuitable for our needs.

Although we improved upon electrophilic aromatic substitution reactions including direct borylation and formylation by using an organolithium approach, chloromethylation at first seems unsuitable to this alternative methodology due to the alkylhalides propensity to react with lithiating reagents. However, a solution presented itself when investigating functionalised monomers, as discussed in chapter 5.

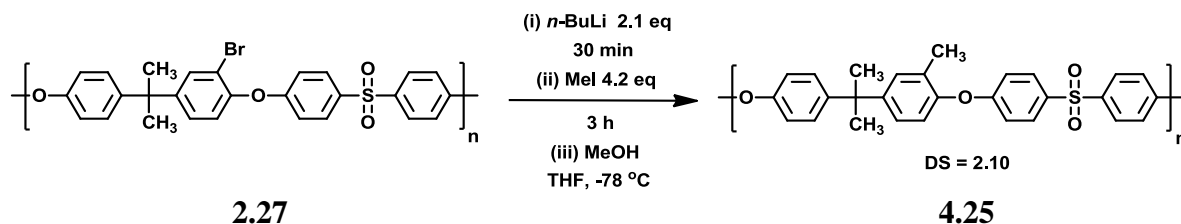
In a patent by Zhang *et al.*<sup>33</sup> bisphenol A was substituted with dimethyl and tetramethyl bisphenol variants in order to polymerise a methylated PSF, as will be discussed in section 5.5. Generally methyl groups are very unreactive so are not an obvious route to further functionalisations. However, the benzylic position created by methylating an aryl group can undergo specific reactions including free radical halogenation. Zhang *et al.* used Br<sub>2</sub> to brominate their methylated PSF with initiation *via* UV irradiation to generate bromomethylated PSF. This produced polymer has equivalent reactivity to its chloromethyl analogue and is able to undergo nucleophilic substitution with a range of nucleophiles.

As an alternative to polymerising methylated monomers, it was envisaged that similar results could be obtained by methylating polysulfone *via* the previously used organolithium approach. Aromatic methylation is commonly achieved by quenching lithiated aromatics with MeI. As such *ortho*-sulfone methylated PSF **4.24** was achieved with high DS by the addition of an excess of MeI to lithiated PSF prepared in the standard fashion, with no adverse side reactions or loss of solubility (**Scheme 4.42**).



Scheme 4.42

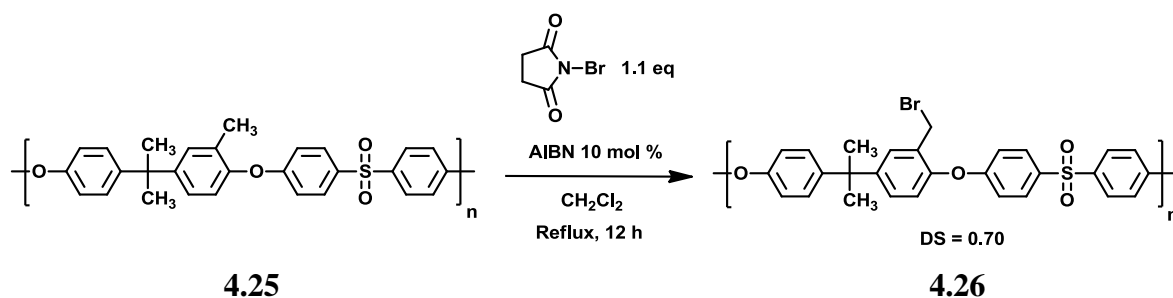
The reaction was also successfully achieved using brominated PSF to generate the *ortho*-ether methylated isomer **4.25** in a degree of substitution up to 2.1 with a minor amount of *ortho*-sulfone product. Moreover, the reaction scaled up to a 15 g scale with the same success (**Scheme 4.43**).



Scheme 4.43

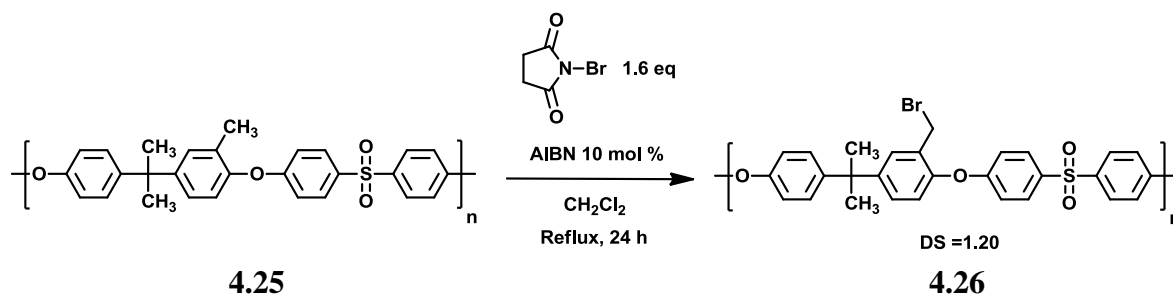
The bromination procedure employed by Zhang *et al.* required use of a large UV lamp and high temperature reflux in tetrachloroethane. Rather than use their methodology, an alternative simpler approach was employed, using azobisisobutyronitrile (AIBN) to initiate the formation of radical bromine from *N*-bromosuccinimide (NBS); a method used extensively within our group.<sup>34</sup>

Initial attempts at the transformation using a typical 2 mol % AIBN and 1.1 equivalents of NBS gave a poor yield. Increasing the amount of AIBN to 10 mol % greatly improved the reaction and afforded bromomethylated PSF **4.26** with a DS of 0.7 (Scheme 4.44).



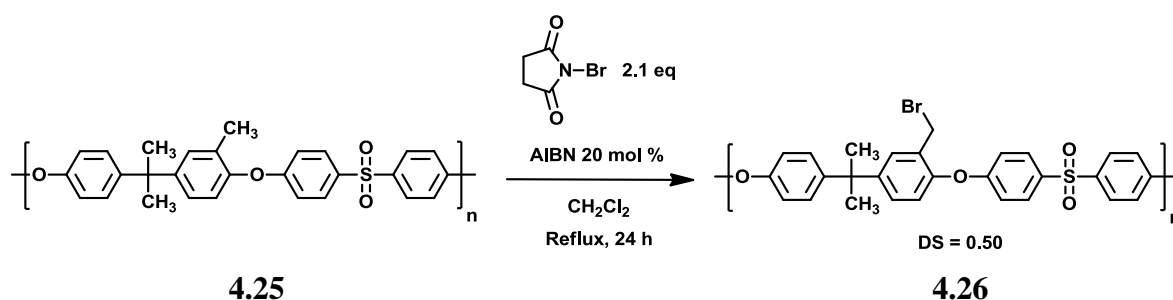
Scheme 4.44

Attempts at improving the already acceptable yield gave interesting results. Increasing the reaction time from 12 to 24 hours immediately gave a large increase in DS (Scheme 4.45).



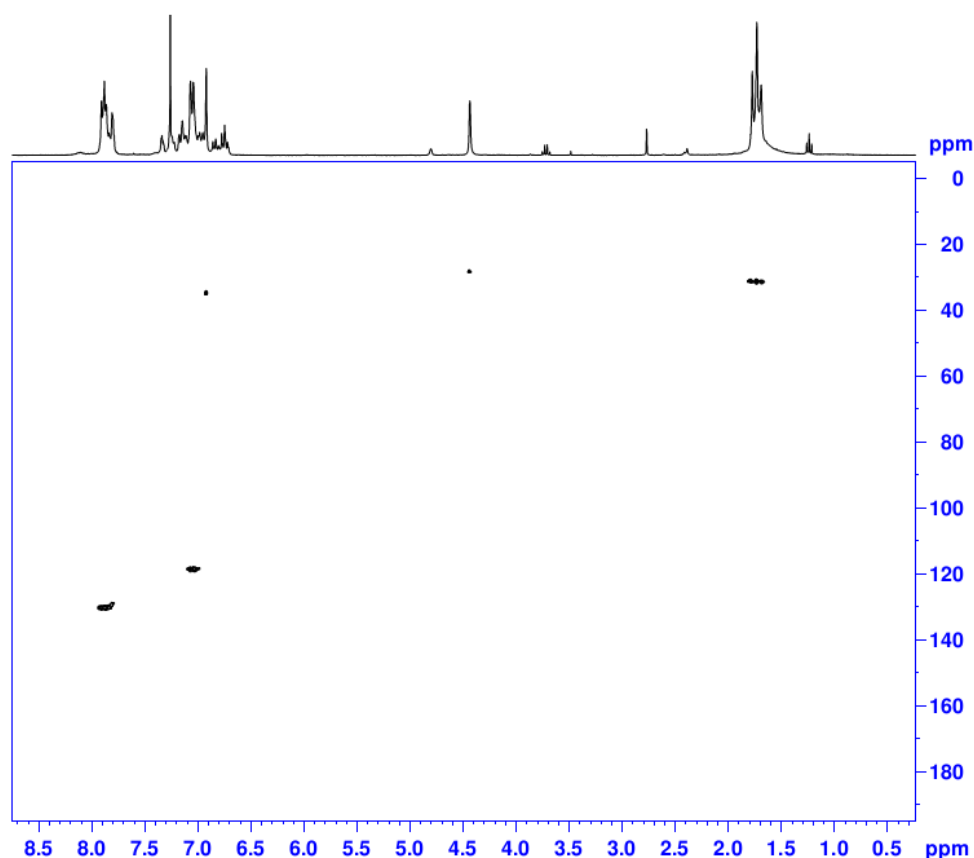
Scheme 4.45

However, attempts to increase the yield still further by increasing the amount of AIBN used to 20 mol % resulted in a reduction in bromination substitution to 50%, a highly unexpected result (**Scheme 4.46**).



Scheme 4.46

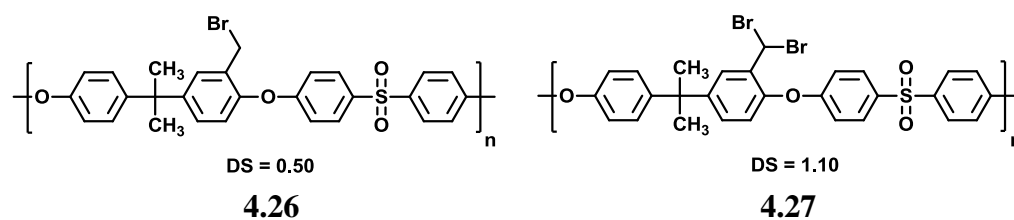
Inspection of the  $^1\text{H}$  NMR spectra showed that the initial methyl peaks at  $\delta 2.1$  and  $\delta 2.4$  ppm had almost completely vanished, indicating that rather than the reaction failing to go to completion, another side reaction must be occurring. Interestingly, a large singlet had appeared at  $\delta 6.92$  ppm in the aromatic region, correlating to a  $\text{CH}/\text{CH}_3$  carbon peak of  $\delta 34.2$  ppm from inspection of the HMQC (**Figure 4.3**) and  $^{13}\text{C}$  Pendent spectra.



**Figure 4.3:** HMQC spectra showing dibromination of methylated PSF.

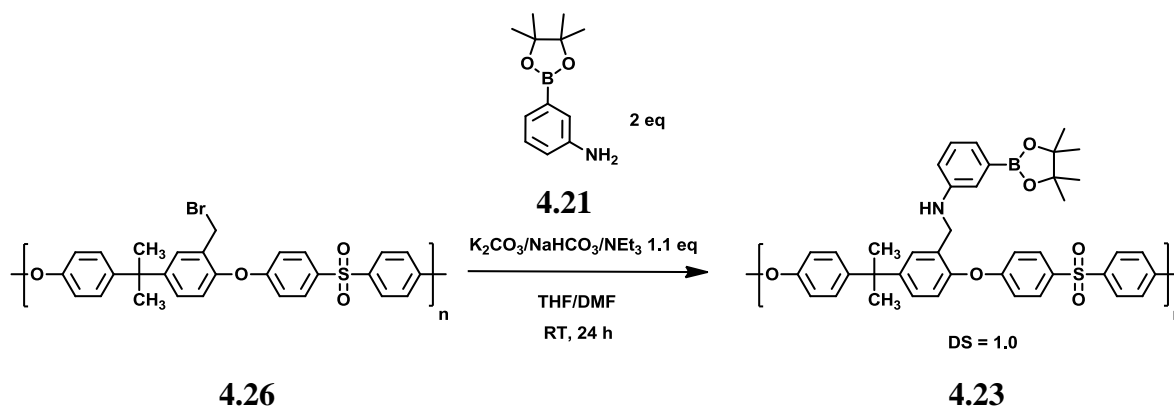
The large upfield shift of the carbon peak in relation to the downfield shift in the  $^1\text{H}$  NMR spectrum indicates that rather than being another aromatic peak, it is a deshielded alkyl group. It was suggested that the increase in brominating reagents used could have led to dibromination of the methyl group, with the errant peak belonging to dibrominated polymer **4.27** of DS 1.1 in addition to the desired monobromination product (**Scheme 4.47**). This hypothesis initially seemed flawed as a carbon in such an environment would be expected to give a signal much further downfield than the  $\delta 34.2$  ppm observed, falling within a range of  $\delta 60$ – $80$  ppm. Literature shows that whilst this is the case with dichlorinated benzyl groups (benzal chlorides), analogous dibrominated benzyl groups appear between  $\delta 35$ – $45$  ppm, in agreement with our data.<sup>35</sup> Fong *et al.*<sup>36</sup> investigated this phenomena, concluding that a combination of hyperconjugative and steric effects give rise to the observed shift in the carbon signal.





Scheme 4.47

Similarly to formylated PSF **3.6**, bromomethylated PSF **4.26** can also react with nucleophiles such as 3-aminophenylboronic acid **4.21**. We investigated a range of solvents and bases to facilitate the transformation and reached a maximum of 100% functionalised borylated PSF **4.23** (DS = 1.0) determined by integration of the pinacol peak in the  $^1\text{H}$  NMR spectra (Scheme 4.48). Similarly to previous polymers, the  $^{11}\text{B}$  NMR spectrum failed to give a signal, but the product tested positive with curcumin dip.

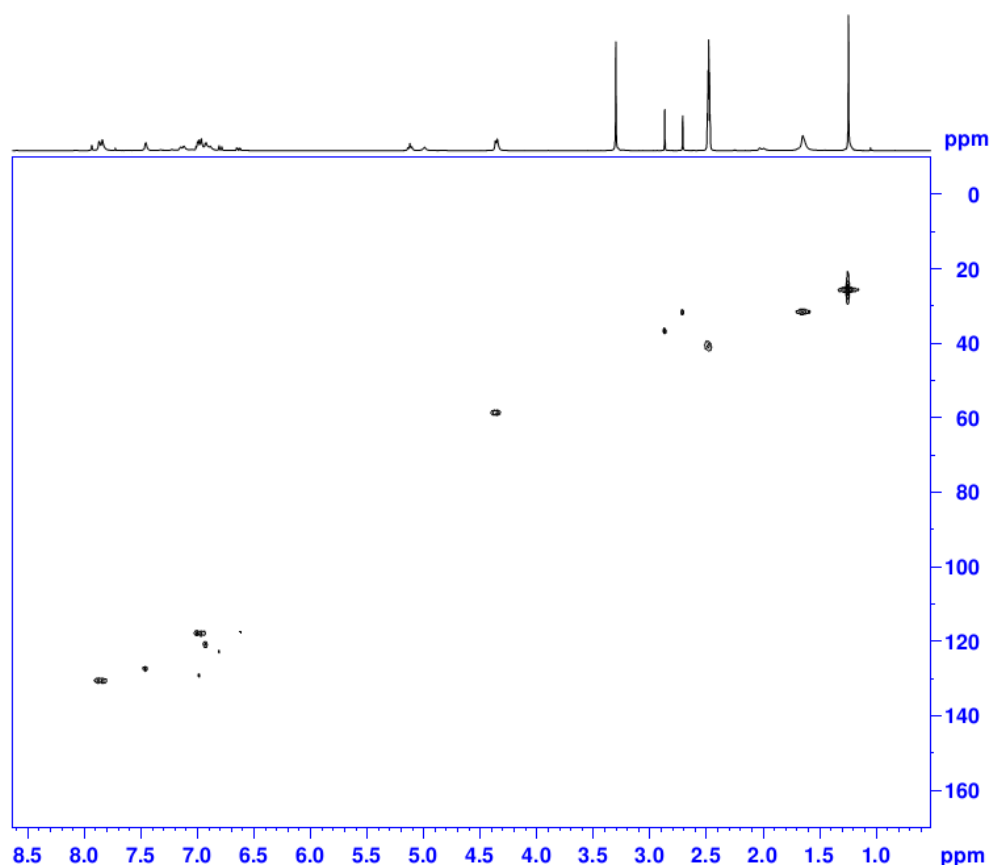


Scheme 4.48

Although the pinacol peak suggests that the reaction was successful, the overall structure was difficult to elucidate from the complicated  $^1\text{H}$  NMR spectra which contained more peaks than expected, suggesting a mixed product. Very broad peaks were also present, partly due to the solubility of the product which varied between experiments. The loss of

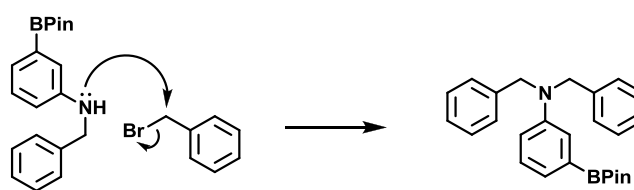
solubility was surprising as the same product produced *via* reductive amination remained  $\text{CHCl}_3$  soluble, whilst the product produced *via* this method was only partly soluble in DMSO. This suggested that another process was occurring such as a cross-linking side reaction, a hypothesis supported by the NMR spectra of the  $\text{K}_2\text{CO}_3$  mediated reaction which produced a cleaner spectrum with fewer peaks than the reactions using  $\text{NaHCO}_3$  and  $\text{NEt}_3$ .

Initial inspection of the  $^1\text{H}$  NMR spectrum suggested a pure product, however the HMQC spectra (**Figure 4.4**) correlated what was thought to be the  $\text{CH}_2\text{-NH-Ar}$  signal at  $\delta 4.36$  ppm with a  $\text{C/CH}_2$  signal at  $\delta 58.01$  ppm in the  $^{13}\text{C}$  Pendent spectrum, a signal much further downfield than expected. It also showed the complete consumption of starting material, as the peak does not correlate to the expected carbon signal at  $\delta 27.81$  ppm as shown in **Figure 4.3**.



**Figure 4.4:** HMQC spectra showing cross-linking of borylated PSF.

Additionally, the integration of the  $\delta 4.36$  ppm  $\text{CH}_2\text{-NH-Ar}$  peak was expected to be in a 1:6 ratio with the 12H pinacol signal at  $\delta 1.25$  ppm and a 2:1 ratio with the 1H aromatic multiplets at  $\delta 6.64$  and  $\delta 6.80$  ppm. However, the integral was twice as large meaning that there were two  $\text{CH}_2\text{-NH-Ar}$  peaks for every attached 3-aminophenylboronic acid pinacol ester. This suggests that the secondary amine linker formed in the reaction is able to react with another bromomethyl group to form a tertiary amine cross-link. This also accounts for the poor solubility (**Scheme 4.49**).



**Scheme 4.49**

A possible solution to this problem is to use a much larger excess of 3-aminophenylboronic acid pinacol ester in order to prevent the secondary reaction from occurring, however the “effective concentration” of the bromomethyl units, as described in section 2.4.3.2, may result in the cross-linking still occurring. Alternately, replacing the amine with a group that cannot undergo subsequent reactions such as a secondary amine or an alcohol may yield better results.

In spite of the failure to cleanly produce a boronic acid appended PSF by this route, we have successfully achieved bromomethylated PSF in a yield, scale and speed far superior to the comparative chloromethylation reaction previously attempted. As such, given more time, the synthetic route designed in section 3.3.2 could be pursued to gain access to boronic acid appended PSF on the scale required for the synthesis of hollow fibre membranes.

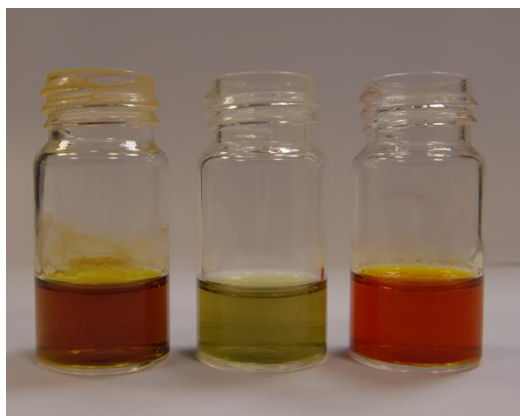
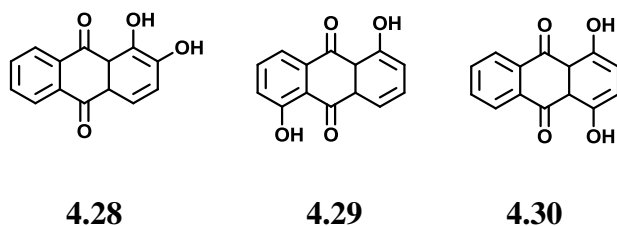
#### 4.10 Model Sugar Separation System

Having synthesised a model boron functionalised polymer to a high yield, its ability to separate sugars was investigated. It was postulated that absorbing the polymer onto silica particles would create a simple boron affinity chromatography system as discussed in section 2.2.5. Neopentyl glycol borate PSF **4.5** was chosen due to the labile nature of the neopentyl glycol protecting group.

Attempts to absorb the polymer onto silica gel for column chromatography unfortunately proved unsuccessful. PSF was readily absorbed *via* evaporation with up to a 1:1 ratio of PSF to silica still giving fine, free-flowing particles suitable for chromatography. However, borylated PSF **4.5** formed large clusters with which a uniform column could not be made. A simple alternative to this issue was to absorb the polymer directly onto a TLC plate to create plates impregnated with boron.

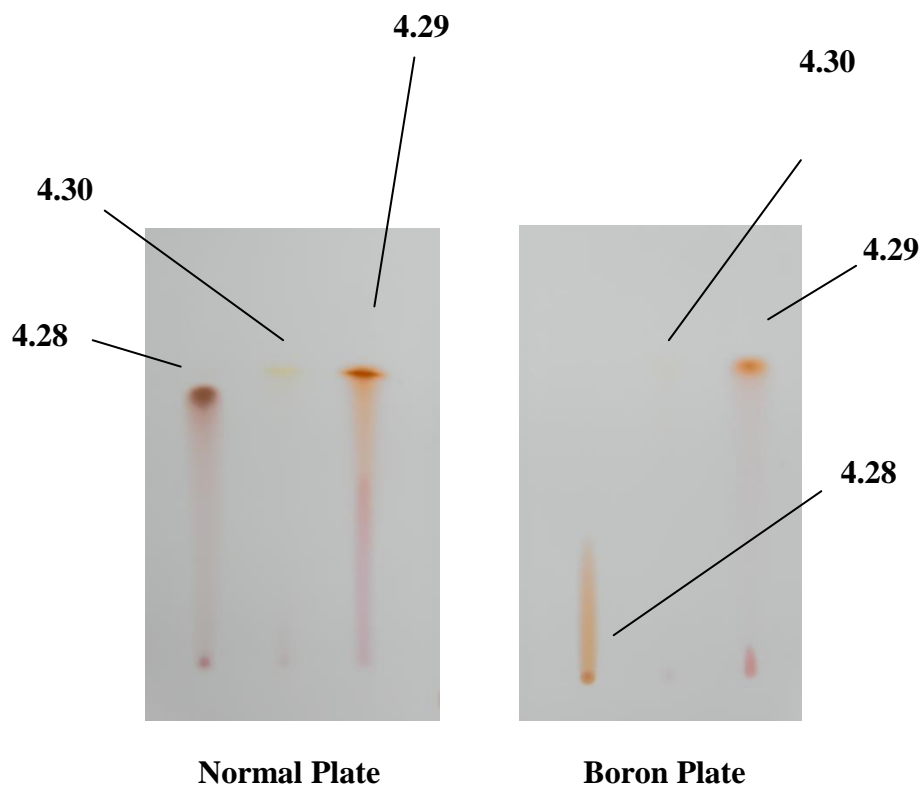
Sugars are difficult to run on TLC plates as they require extremely polar solvent systems and visualisation stains that may not be compatible with the produced boron plates, therefore a more suitable 1,2-diol was used as a substitute. Alizarin **4.28**, otherwise known as 1,2-dihydroxyanthraquinone, was chosen as its distinct brown colour makes it perceptible on TLC plates without further visualisation and as a 1,2-diol, it readily binds to boronic acids. It is speculated that alizarin will bind to the boronic acid coated to the TLC plate, retarding its progress when the plate is run. Therefore alizarin will have a much lower  $R_F$  on a boron plate than a regular silica plate.

The control compounds chosen were 1,5-dihydroxyanthraquinone **4.29** and 1,4-dihydroxyanthraquinone **4.30** (**Figure 4.5**). They are both isomers of alizarin and have near identical  $R_F$  values when run on a standard silica TLC plate. They are also brightly coloured, yellow and orange respectively, allowing easy distinction between the 3 compounds. However, they do not possess the necessary 1,2-diol functionality to bind to boronic acids, and thus should have much larger  $R_F$  values than alizarin on the boron plates.



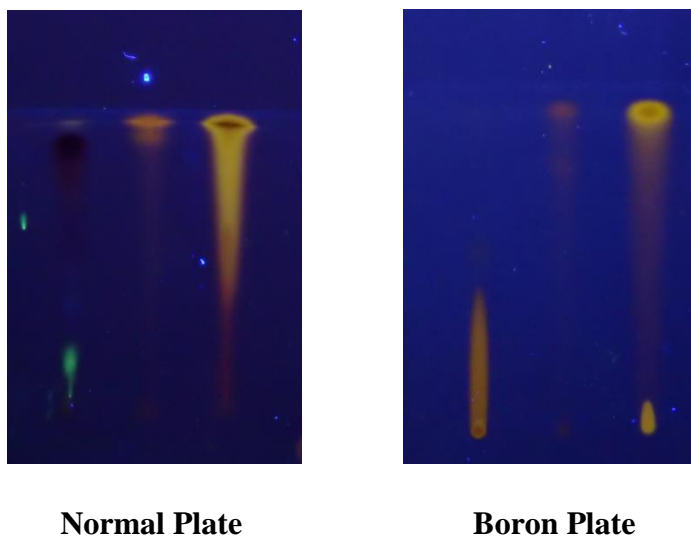
**Figure 4.5:** 1,2-dihydroxyanthraquinone (left), 1,5- dihydroxyanthraquinone (centre) and 1,4- dihydroxyanthraquinone (right) solutions.

To prepare the boron containing plates, TLC plates averaging 35 mm x 65 mm in size, were soaked in a solution of 1 mgml<sup>-1</sup> PSFNeo DS = 1.0 for 5 minutes followed by air drying for a further 10 minutes. The anthraquinones were dissolved to saturation in acetone and spotted onto both the boron and standard silica TLC plates with glass capillary tubes to minimise spot size. TLC plates were run eluting with 6:4 ethyl acetate/petroleum ether. As expected, minimal separation was observed using a regular silica plate. However, under the same solvent system using our boron plates, whilst the  $R_F$  of 1,4-dihydroxyanthraquinone and 1,5-dihydroxyanthraquinone did not change, alizarin was separated by a large degree, mostly remaining on the base line with some smearing suspected due to impurities within the alizarin sample (**Figure 4.6**).



**Figure 4.6:** Separation of diols on normal TLC plate versus boron TLC plate.

The alizarin is clearly binding to the boronic acid and thus having its progress retarded. This becomes more apparent by visualising the plates with longwave UV (366 nm) as shown in **Figure 4.7**.



**Figure 4.7:** Visualisation of TLC plates under 366nm UV light.

Evidently, 1,4-dihydroxyanthraquinone and 1,5-dihydroxyanthraquinone are fluorescent under excitation at this wavelength whereas alizarin is not. However, upon binding to boron on our boron TLC plate, the resultant alizarin-boron complex becomes highly fluorescent.

This simple experiment demonstrates that a boron appended PSF can be used to preferentially separate 1,2-diol compounds from an isomeric mixture. Whilst the separation has only been shown on an analytical scale, there is potential for further practical separations if the difficulties forming uniform boron coated silica gels are overcome.

Overall we have proved that the principle of the project is viable, with this strong evidence that an equivalent boron appended hollow fibre membrane system would separate a similar diol system.

#### 4.11 Conclusion and Future Work

In this chapter we investigated the use of organolithium reagents to mediate the functionalisation of PSF. Comparatively to the previously attempted electrophilic aromatic substitution routes, the organolithium methods were much more successful.

Direct borylation *via* *n*-BuLi provided a useful reactive intermediate for future reactions, as well as a potential model compound for sugar separation, as shown by our successful TLC separation of alizarins using boron doped plates. This potential separation ability requires further research through hollow fibre synthesis or potentially simpler separation techniques such as more complex chromatography.

Despite the epoxide ring opening reaction and the reaction with aldehydes suffering from solubility problems they both worked to an extent and could be viable methods with alternative reagents. Considering that the non-boronic ester functionalised aldehyde reaction worked successfully it is possible a two stage approach of functionalisation, followed by boronic acid installation may yield a soluble product.

Formylation and bromomethylation reactions both provided straightforward routes to highly functionalised polymers capable of undergoing a range of further transformations, with the bromomethylation route being a great success, providing an alternative route to halomethylated PSF without the need for large amounts of the toxic reagents commonly used. Carboxylation is equally a third suitable route providing one has access to the right equipment. Whilst the scope of subsequent functionalisations to achieve the desired boronic acid appended polymer has not been fully demonstrated, the concept has been proven and some simple tethered boronic acid polymers have been successfully produced.

We have successfully completed our initial aim in functionalising PSF cleanly and on a large multigram scale *via* several different reactions. We have successfully demonstrated subsequent functionalisations to incorporate the desired boronic acid functionality, with and without a linker. In the future, different linkers could be included by altering the reagents used.

Additionally, using the lithiation methodology we have the desirable ability to precisely control the degree of functionalisation. This could be useful to vary the degree of substitution of boronic acid, depending on the levels required for sugar separation should



adjustments be required after the properties of the final membrane have been investigated. This precise control of the degree of substitution is in stark contrast to the electrophilic aromatic substitution routes to functionalise PSF commonly found in literature.

Precedence exists for converting halomethylated PSF into the azido derivative as well as the subsequent “click” reactions of the azidomethylated PSF with a variety of alkynyl reagents to give more complex functionalization. This was the initial route to a functionalised polymer we designed in section **3.3.2**, with only the inability to safely synthesise chloromethylated PSF halting the line of research. However, the superior, safer bromomethylation route will allow us in future to complete it, giving us the modularly functionalised boronic acid polymer we desire.

#### 4.12 References

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## Chapter 5 : Functional Monomer Polymerisation

### 5.1 Introduction

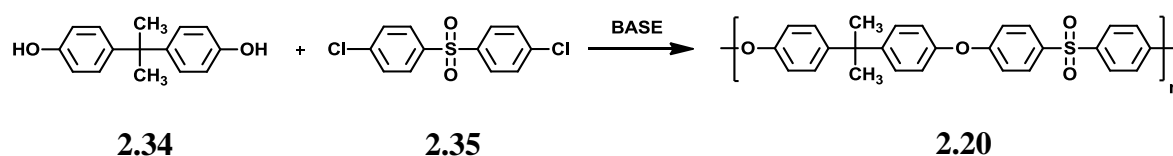
The following chapter discusses the routes and attempts to synthesise a functional PSF *via* the polymerisation of functional monomer units.

### 5.2 General Synthesis of Polysulfone

Poly(arylene ether) type polymers such as polysulfone can be synthesised *via* electrophilic aromatic substitution reactions such as Friedel-Crafts sulfonylation polymerisation<sup>1,2</sup>, base initiated nucleophilic aromatic substitution<sup>3,4</sup> or metal mediated routes such as Ullman coupling.<sup>5</sup>

The nucleophilic aromatic substitution route ( $S_NAr$ ) has proven to be the most successful, giving linear, high molecular weight polymers, with the polymerisation tolerating a wide range of functional groups and not producing the mechanically poor branched side products associated with other methods.<sup>6,7</sup>

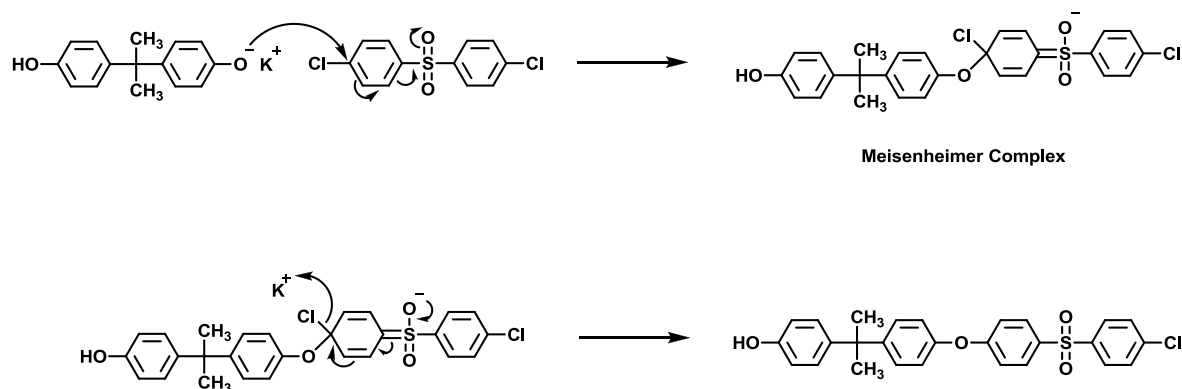
The reaction is a step-growth polycondensation, typically between bisphenol A **2.34** and 4,4'-dichlorodiphenyl sulfone **2.35**, conducted in refluxing aprotic solvent with an alkali base (**Scheme 5.1**).



**Scheme 5.1**

Initially the bisphenol reacts with a stoichiometric amount of base to form a phenolate salt, with the process forced by the continuous azeotropic removal of water by refluxing a layer

of toluene on top of the aprotic solvent layer using a Dean Stark apparatus, with relatively anhydrous conditions required to prevent hydrolytic side reactions. Whilst strong bases such as NaOH were initially used, it was found that they promoted the unwanted conversion of the bishalide sulfones into bisphenols thus lowering the molecular weight of the polymer produced, with weaker bases such as  $K_2CO_3$  found to be superior.<sup>8</sup> Once formed the phenolate can nucleophilically attack the activated diphenyl sulfone, substituting for the halide through a so called Meisenheimer Complex before eliminating as an alkali salt. Aprotic solvents such as DMSO or NMP are required in order to solubilise the monomers, salts and produced polymer simultaneously, as well as for their ability to stabilise the formed intermediates. The postulated mechanism for the initial dimer formation is shown in **Scheme 5.2**.<sup>6</sup>

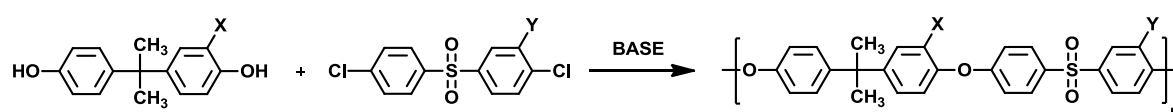


**Scheme 5.2**

As a step-grow process, the polymerisation progresses as the produced dimers react together or with other monomers to form trimers and oligomers which continue to react, eventually producing polymers. As only one reactive step is responsible for the polymerisation, the rate for each condensation is the same, thus the overall molecular weight of the polymer steadily increases throughout the reaction, though this means a high overall conversion of monomer to polymer is required to obtain a large molecular weight.<sup>9</sup>

### 5.3 Functionalised Monomers

In the previous chapters we have discussed ways of directly functionalising PSF, to varying degrees of success. As discussed in section 2.3.3.3, rather than attempt to functionalise the relatively unreactive PSF it is possible to functionalise the comparatively reactive monomeric precursors. Alternatively, a range of functional monomers are commercially available. The chosen functional monomer can then be substituted for the equivalent non-functionalised monomer in the polymerisation process shown in section 5.2 which would result in functional polymer being formed (**Scheme 5.3**).



**Scheme 5.3**

With our goal of replicating the hollow fibre technology previously produced by the Perera group as discussed in section 2.3.1, our produced functional polymer is required to be as close to the molecular weight and polydispersity of Udel PSF as possible. As such, the functionalised monomer is required to not have detrimental effect on the polymerisation process i.e. the functional group cannot compete with or lower the reactivity of the polymerisation.

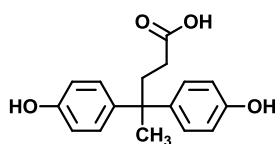
The choice of functionalisation must be carefully considered. Addition of alcohol or halogen groups directly to either monomer could cause polymerisation to occur at the newly functionalised *ortho* or *meta* position rather than the desired *para*, resulting in the formation of undesired branched polymers. This is could also be the case with other nucleophilic groups such as amines which might compete with the  $S_NAr$  process. How the monomers can be functionalised also varies between the two. The reactivity of the diphenylsulfone unit comes from the dual electron withdrawing and resonance stabilising effect of the sulfone moiety. This means that functionalisation with an electron donating group such as a methoxy or amine may lower the reactivity of the disulphone by disrupting and destabilizing the Meisenheimer transition state. Conversely, addition of an electron

withdrawing group to bisphenol A would deactivate the produced phenolate ion, potentially worsening its ability to act as nucleophile.

With this information, it was predicted that functionalisation of bisphenol A would be less likely to decrease the ability of the monomer to polymerise than functionalisation of the diphenylsulfone, due to the complex resonance involved in its reactivity. As such, we started by investigating commercially available bisphenol A analogues.

#### 5.4 Polymerisation with 4,4-Bis(4'-hydroxyphenyl)pentanoic acid

After checking the commercial availability of a range of bisphenol A analogues, 4,4-bis(4'-hydroxyphenyl)pentanoic acid **2.36** immediately stood out as being suitable.

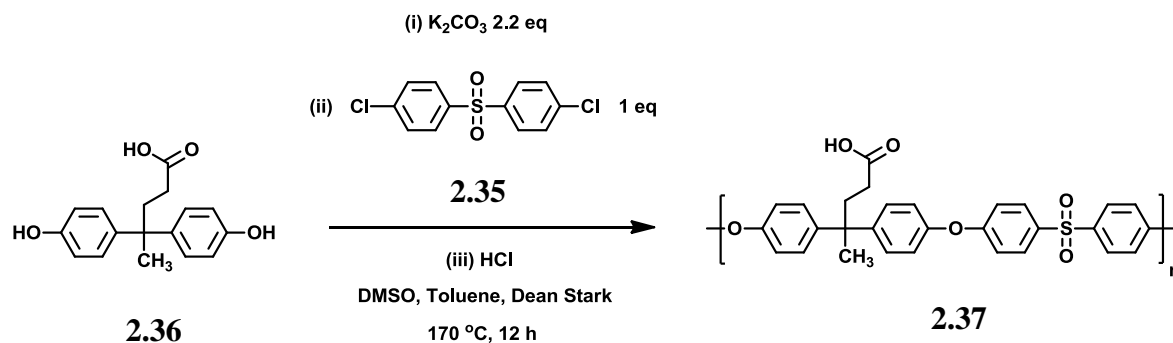


**2.36**

As discussed in section 4.7, carboxylic acids are excellent functional groups for our needs; able to undergo peptidic coupling or acid chloride mediated substitution reactions in order to achieve further functionalisation. Not only is the carboxylic acid attached by a flexible tether, which is desirable to achieve a proper functional carrier system as discussed in section 2.3.3, but it is functionalised at the gem-dimethyl group rather than directly to the phenyl ring meaning that any negative electronic effects should not influence the phenols reactivity. There is a concern that the carboxylic acid itself could interfere with the polymerisation process either by reacting with the  $K_2CO_3$  or by interacting with the  $S_NAr$  intermediate, however these fears were allayed by the work of Ritter *et al.*<sup>10</sup> who successfully used 4,4-bis(4'-hydroxyphenyl)pentanoic acid in lieu of bisphenol A to synthesise carboxylic acid functionalised PSF **2.37**.

We attempted the polymerisation following the conditions put forward by Ritter *et al.* To a solution of 4,4-bis(4'-hydroxyphenyl)pentanoic acid **2.37** dissolved in a mixture anhydrous

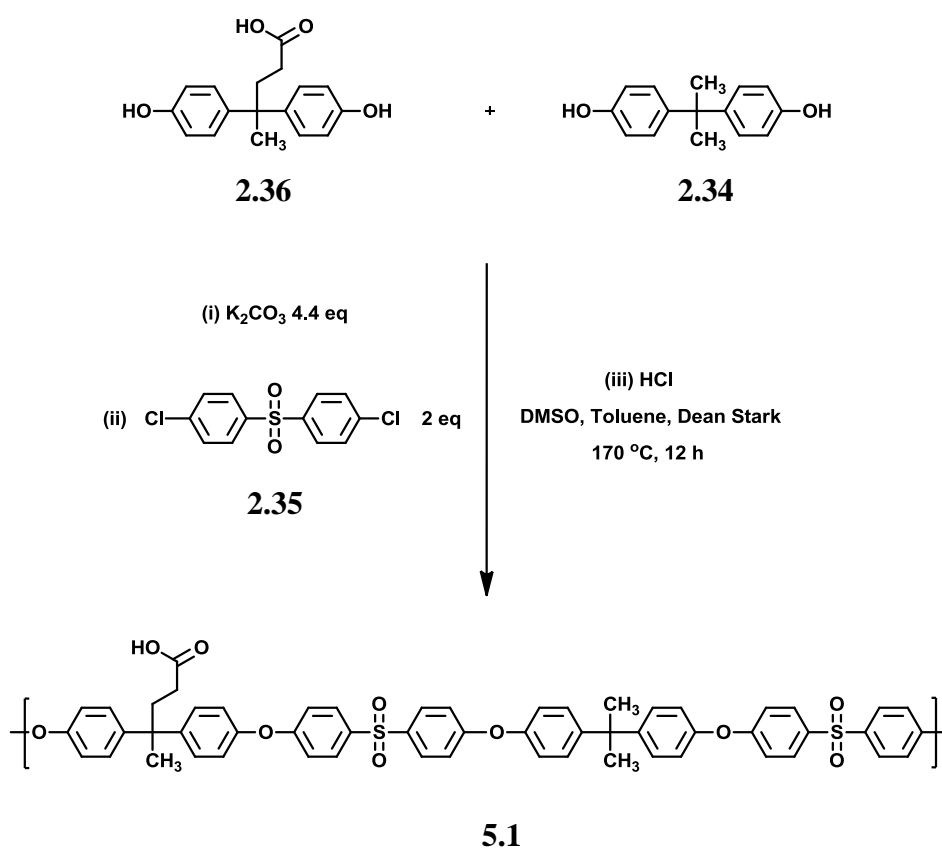
DMSO and toluene was added 2.2 equivalents of  $K_2CO_3$  followed by attachment of a Dean Stark apparatus. The mixture was then refluxed for 2 hours, azeotropically removing water from the reaction and forming the potassium phenolate salt, whereupon 1 equivalent of 4,4'-dichlorodiphenyl sulfone was added and the reaction mixture refluxed for a further 10 hours before quenching with concentrated HCl (**Scheme 5.4**).



Scheme 5.4

By using equal amounts of both monomers a 100% functionalised polymer was achieved. We also produced a 50% functionalised polymer **5.1** by replacing half of the used 4,4-bis(4'-hydroxyphenyl)pentanoic acid with bisphenol A (**Scheme 5.5**).





Scheme 5.5

The two produced polymers appeared as a light brown powder and gave clean  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra as expected. Whilst the NMR spectra show the level of functionalisation of the polymer, they do not give information on other polymer properties such as chain length or polydispersity. With our previous functionalisation attempts this was not an issue as the modification processes were chosen specifically to not affect these properties of Udel PSF. However, as we are conducting our own polymerisation process, these properties become variables and must be quantified, which can be achieved *via* gel permeation chromatography (GPC). Ideally, we require the functionalised polysulfones to be as near to Udel PSF in properties as possible.

Generally the three properties we are interested in are;<sup>11</sup>

- The number average molecular weight ( $M_n$ ): Simply the total weight of the polymer present divided by the number of molecules to give a traditional average.
- The weight average molecular weight ( $M_w$ ): Is an average weighted towards molecular weight, as larger polymer chains will contribute more towards the total molecular weight than smaller ones.
- The polydispersity (PD): Is equal to  $M_w/M_n$ . This number represents the diversity in polymer chain size. When the PD is equal to 1 the compound is entirely made of one size of polymer chain and is thus monodisperse. When the PD is greater than 1 it means that there is a distribution of differently sized polymers, with this diversity increasing proportionally with PD.

These three properties effectively tell us the size of the polymer and how uniform its structure is.

The initial attempt at polymerising functionalised PSF **2.37** and **5.1** gave a polymer with the following properties measured in Daltons. The properties of PSF **2.20** are also shown for comparison. (**Table 5.1**).

| Polymer           | $M_n$ / Da | $M_w$ / Da | PD   |
|-------------------|------------|------------|------|
| PSF <b>2.37-1</b> | 1900       | 2600       | 1.36 |
| PSF <b>5.1</b>    | 2400       | 2700       | 1.14 |
| PSF <b>2.20</b>   | 87150      | 46200      | 2.08 |

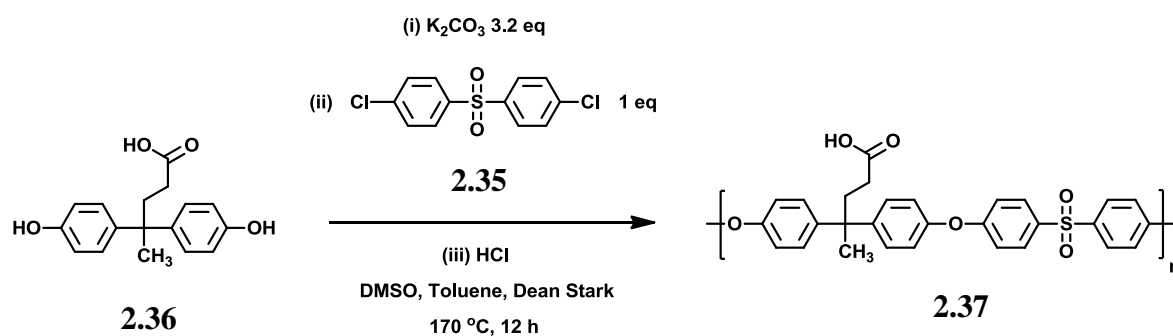
**Table 5.1:** Properties of synthesised PSF **2.37-1** and PSF **5.1** versus PSF **2.20**.

In comparison to the desired properties of PSF **2.20**, both the 100% and 50% functionalised PSFs are very small polymers to the point where they are considered oligomers rather than polymers. A subsequent publication by Ritter *et al.*<sup>12</sup> measured the molecular weight of their polymers at 3,500 Da using MALDI-TOF mass spectrometry, which is consistent with our results using their procedure. Evidently these oligomers were far too small to be of use to us, therefore we needed to investigate a means to increase the overall polymer size produced by this method.

Using a comparative method to the one used above, Charoensirisomboon *et al.*<sup>13</sup> synthesised chlorine end group terminated PSF by using a slight excess of dichlorodiphenylsulfone with bisphenol A. According to the Carothers Equation regarding step-growth polymerisation, when one monomer is in stoichiometric excess of another, the minority monomer becomes the limiting reagent to the polymerisation and thus reduces the overall degree of polymerisation.<sup>14</sup> In spite of this, the PSF produced had a  $M_n$  of 5,700, a  $M_w$  of 28,800 and a resultant PD of 5.05 and thus is a much larger polymer than the ones we synthesised. This suggests that the carboxylic acid group is interfering with the polymerisation process as feared.

An immediate problem with Ritter's synthesis was identified as the amount of base used. One of the major factors in creating high molecular weight PSF *via* the  $S_NAr$  method is that at least 2 equivalents of base must be used in order to generate the needed diphenoxylate salt.<sup>6</sup> Whilst Ritter *et al.* used a slight excess in relation to the two phenol groups of the monomer, they did not take into account the carboxylic acid. As carboxylic acids are much stronger acids than phenols, with a  $pK_a$  of around 5 vs. 10 for that of phenols, it is suspected that the base is preferentially deprotonating the carboxylic acid over the phenol thus reducing the overall amount of free base in the reaction mixture and retarding the formation of the reactive monomers. We postulated that by increasing the amount of  $K_2CO_3$  in the reaction to include a sacrificial equivalent for the carboxylic acid that we may achieve a higher molecular weight polymer.

We repeated the conditions used in **Scheme 5.4** with the 2.2 equivalents of  $K_2CO_3$  increased to 3.2 (**Scheme 5.6**).



Scheme 5.6

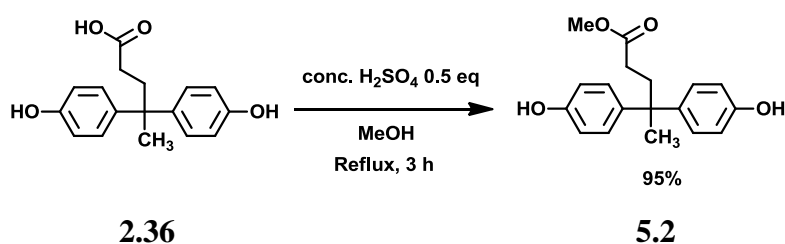
These new conditions showed an immediate improvement over the previous method, more than doubling the size of the polymer produced (**Table 5.2**).

| Polymer           | $M_n$ / Da | $M_w$ / Da | PD   |
|-------------------|------------|------------|------|
| PSF <b>2.37-2</b> | 6700       | 5700       | 1.21 |

Table 5.2: Properties of synthesised PSF **2.37-2**.

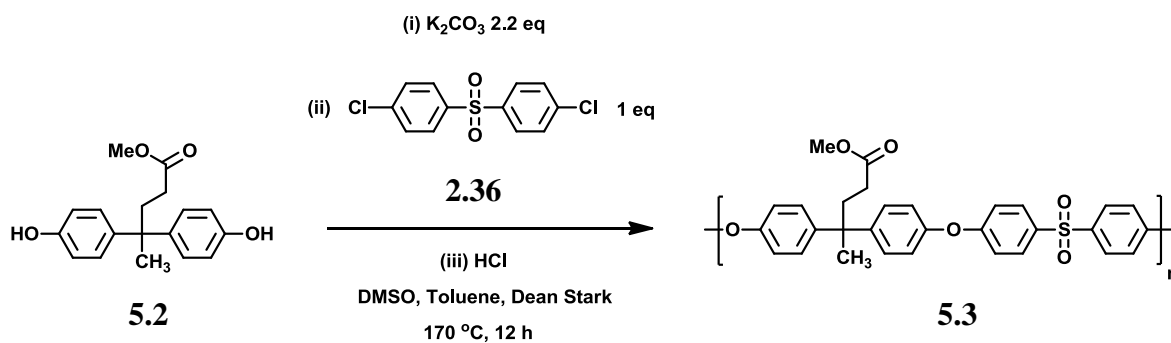
Another solution to the problem of the carboxylic acid interfering with the polymerisation was to convert it into a methyl ester. Esters are much less reactive than the carboxylic acids and shouldn't require extra base, so are potentially more suited to the polymerisation process. Additionally they still possess enough reactivity to facilitate further functionalisation and can easily be converted back into carboxylic acids if needed once polymerised.

We first synthesised 4,4-bis-(4-hydroxyphenyl)pentanoic acid methyl ester **5.2** by refluxing 4,4-bis-(4-hydroxyphenyl)pentanoic acid **2.36** in MeOH with concentrated  $\text{H}_2\text{SO}_4$  for 3 hours (**Scheme 5.7**).



Scheme 5.7

The synthesised methyl ester was then polymerised using the initial set of conditions, with only 2.2 equivalents of  $\text{K}_2\text{CO}_3$  required (**Scheme 5.8**).



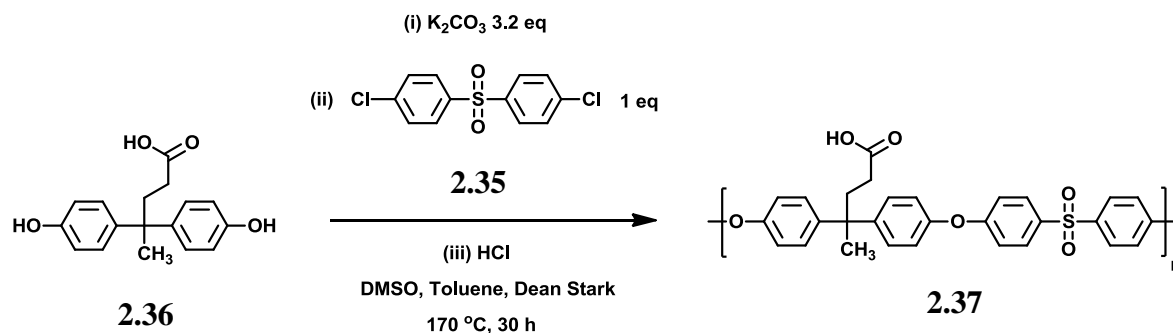
Scheme 5.8

Whilst the methylated ester did result in an improved polymer in comparison to our original attempts, it was marginally smaller than the PSF produced in **Scheme 5.6**, suggesting that either the methyl ester was inferior to the carboxylic acid providing enough base is present, or that a greater amount of base in general improves the yield of the reaction (**Table 5.3**).

| Polymer        | $M_n$ / Da | $M_w$ / Da | PD   |
|----------------|------------|------------|------|
| PSF <b>5.3</b> | 3550       | 5250       | 1.49 |

**Table 5.3:** Properties of synthesised PSF **5.3**.

In order to improve the reaction further still, we repeated the conditions from **Scheme 5.6** with an increased reaction time of 30 hours (**Scheme 5.9**). It was noted that another important factor in achieving a high molecular weight polymer was the efficient removal of water from the reaction mixture. As such the initial azeotrope was extended to 6 hours and stringent care was taken to maintain as close to anhydrous conditions as possible. We initially attempted to undertake the reflux under an atmosphere of nitrogen, however creating a sealed system created too much pressure, causing the dean stark to become slightly raised and allowing the refluxing toluene to escape. Instead we settled on flushing the system with nitrogen before use and attaching a drying tube filled with anhydrous calcium chloride to ensure the atmosphere remained dry.

**Scheme 5.9**

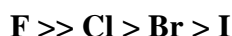
These conditions resulted in another marked increase in the molecular weight of the polymer produced (**Table 5.4**).

| Polymer           | M <sub>n</sub> / Da | M <sub>w</sub> / Da | PD   |
|-------------------|---------------------|---------------------|------|
| PSF <b>2.37-3</b> | 6200                | 9450                | 1.52 |

**Table 5.4:** Properties of synthesised PSF **2.37-3**.

Again, whilst these conditions were a significant improvement over those reported by Ritter *et al.*, the produced polymer is a full factor of 10 smaller than the commercial Udel PSF and therefore wholly unsuitable for our needs. With the reactants we are using the conditions have been optimised as far as reasonably possible, indicating that if the polymerisation is to be improved further that the reactants need altering.

Perhaps the simplest change of reagents would be to replace 4,4'-dichlorodiphenyl sulfone with an analogue containing a different halogen in place of chlorine. As the reaction involves nucleophilic substitution it would be logical to conclude that replacing chlorine with a better leaving group such as bromine or iodine would improve the reaction. However, the opposite occurs, with the following order of reactivity of dihalodiphenyl sulfones observed (**Figure 5.1**).<sup>6</sup>

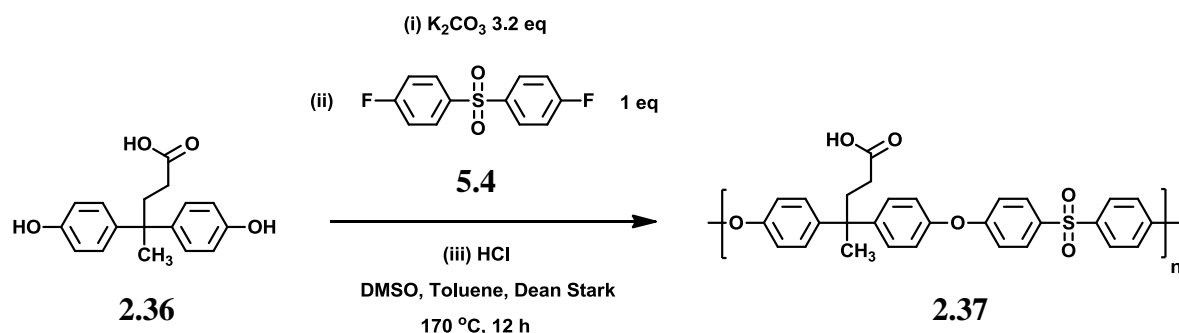


**Figure 5.1:** Reactivity series of halide leaving groups.

This is surprising as due to the strength of carbon-fluorine bonding fluorine is the worst leaving group by a wide margin. This is explained by looking at the mechanism for the reaction, with the nucleophilic attack being the rate-determining step and the eventual substitution of the halogen occurring comparatively rapidly. Fluorine is therefore favoured for its ability to stabilise the Meisenheimer intermediate as well as increasing the electrophilicity and thus reactivity of the carbon it is attached to.

We initially attempted the polymerisation using 4,4'-difluorodiphenyl sulfone **5.4** under the standard conditions we had established, azeotroping the bisphenol and K<sub>2</sub>CO<sub>3</sub> for 2

hours before addition of the fluoro monomer and refluxing for a further 10 hours (**Scheme 5.10**).



**Scheme 5.10**

Upon precipitation of the polymer, rather than the brown powder recovered previously a thick mass of white fibrous material was obtained. This precipitate strongly resembled Udel PSF in its precipitated state and was a good sign that the polymer produced had a high molecular weight. This was found to be the case, and the reaction was repeated a number of times to judge the consistency of the molecular weights it produces (**Table 5.5**).

| Polymer           | $M_n$ / Da | $M_w$ / Da | PD   |
|-------------------|------------|------------|------|
| PSF <b>2.37-4</b> | 6500       | 10950      | 1.69 |
| PSF <b>2.37-5</b> | 12000      | 18600      | 1.55 |
| PSF <b>2.37-6</b> | 18450      | 28650      | 1.56 |
| PSF <b>2.37-7</b> | 13050      | 20950      | 1.61 |

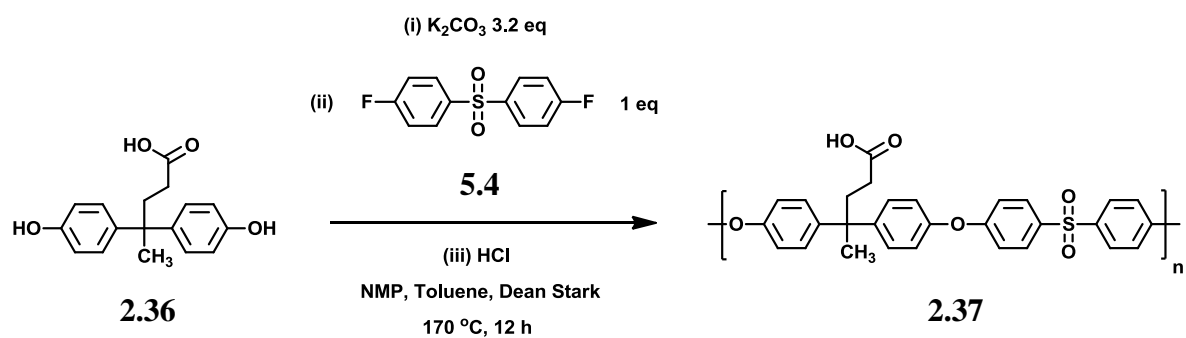
**Table 5.5:** Properties of synthesised PSF **2.37-4**, PSF **2.37-5**, PSF **2.37-6** and PSF **2.37-7**.

The results whilst somewhat inconsistent are exponentially better than those produced by the dichloro analogue, especially considering the comparatively short reaction time. These



positive preliminary results indicate that 4,4'-difluorodiphenyl sulfone has the potential to generate a polymer of the desired size and further investigation was undertaken. It should be noted that there are two major downsides to these conditions; cost and the production of side products. 4,4'-difluorodiphenyl sulfone is much more expensive than the chloro isomer resulting in an increased overall cost of the polymerisation. Additionally, instead of producing harmless KCl as a side product large amounts of KF are generated, requiring careful handling and etching any glassware used.

In order to improve the molecular weight still further it was suggested to switch the solvent from DMSO to NMP. Not only is NMP generally a better solvent for PSF but its higher boiling point means the overall temperature of the reaction can be increased if necessary. In addition the azeotrope time was increased from 2 hours to 6 hours as this previously gave a positive effect, with the overall reaction consisting of 6 hours azeotrope and 6 hours reflux. Pleasingly this had the desired effect, increasing polymer size threefold. Again, multiple runs of the reaction were attempted to gauge reproducibility (**Scheme 5.11**).



**Scheme 5.11**

The polymers produced under these conditions are approaching the desired size and polydispersity as to be comparable to PSF as required, though again there is a moderate variance between runs which will need to be addressed (**Table 5.6**).

| Polymer            | $M_n$ / Da | $M_w$ / Da | PD   |
|--------------------|------------|------------|------|
| PSF <b>2.37-8</b>  | 37100      | 64200      | 1.73 |
| PSF <b>2.37-9</b>  | 23600      | 41400      | 1.76 |
| PSF <b>2.37-10</b> | 23800      | 51300      | 2.15 |

**Table 5.6:** Properties of synthesised PSF **2.37-8**, PSF **2.37-9** and PSF **2.37-10**.

Whilst it is probable that a lengthened reaction time would increase the polymer size further, another variable was first investigated in the hopes of achieving the desired increase whilst maintaining the short reaction time.

As previously mentioned, aprotic solvents are required in order to maintain solvation of the starting monomers, the produced polymer and the intermediate salts, with poor yields resulting when solubility is low. Toluene is a necessary additive to the polymerisation process in order to azeotropically remove water which would retard the reaction. PSF is however very insoluble in toluene, therefore it was postulated that its presence in the reaction mixture may actually lower the molecular weights obtained. Ideally the toluene could be replaced with a solvent capable of azeotroping water whilst also solvating PSF. Unfortunately out of the solvents PSF is soluble in,  $\text{CHCl}_3$ , DCM and THF will azeotrope water but have too low a boiling point to be realistically used and DMF, DMAC, DMSO and NMP whilst having a suitable boiling point are not capable of forming azeotropes with water.<sup>15</sup>

A solution to this issue was presented by Dai *et al.*<sup>16</sup> who polymerised 3,3',5,5'-tetramethylbisphenol A with 4,4-difluorodiphenylsulfone in order to generate a tetramethylated PSF. For their polymerisation process, after a similar length of azeotrope time they proceeded to remove the toluene layer by emptying the Dean Stark trap before continuing to reflux for another 4 hours. Removal of the toluene increases the produced polymers solubility in the reaction mixture, allowing larger molecular weights to be generated, as indicated by a marked increase in the viscosity of the solution. This indicates that the azeotropic removal of water is only a major concern during phenolate formation stage and is not necessary during the polymerisation step.

We therefore repeated the conditions used in **Scheme 5.11**, stopping the reaction to remove the toluene layer upon completion of the azeotrope after 6 hours, before continuing the reflux for the remaining time. In accordance with the literature precedence, there was a notable increase in viscosity of the solution (**Table 5.7**).

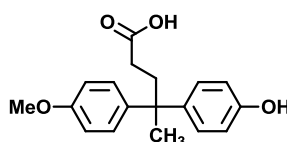
| Polymer            | $M_n$ / Da | $M_w$ / Da | PD   |
|--------------------|------------|------------|------|
| PSF <b>2.37-11</b> | 46350      | 98700      | 2.13 |
| PSF <b>2.37-12</b> | 37850      | 255300     | 6.75 |
| PSF <b>2.37-13</b> | 52700      | 142150     | 2.70 |
| PSF <b>2.37-14</b> | 110050     | 155500     | 1.41 |

**Table 5.7:** Properties of synthesised PSF **2.37-11**, PSF **2.37-12**, PSF **2.37-13** and PSF **2.37-14**.

Initially these conditions appeared perfect, with PSF **2.37-11** having near identical properties to Udel PSF. However upon repetition the generated polymers were very inconsistent, producing much larger chain sizes. This variance in polymer size has been present throughout the optimisation process, though it was much less when dealing with smaller polymers. Evidently the problem increases in line with an increase in polymer size. This is of major concern as different sized polymers will have different spinning properties when constructing hollow fibres thus the polymers need to be as consistent as possible.

It is suspected that this variance comes from inconsistencies in the mixing process. As the reaction progresses and polymer is produced, the viscosity of the mixture increases and the efficiency of the magnetic stirring becomes difficult to maintain, with the speed of the mixing hard to accurately control. Whilst this is only a minor issue at small polymer sizes, once the polymers become large the viscosity increases, further decreasing the control over the speed of the mixing. At this point minor differences between the size of the flask or magnetic stirrer bar used as well as ability of different stirring mantles result in widely inconsistent levels of mixing, thus producing variably sized polymers. An obvious solution is to use a mechanical overhead stirrer, able to be set to a specific and consistent rpm. This equipment was unfortunately unavailable to us.

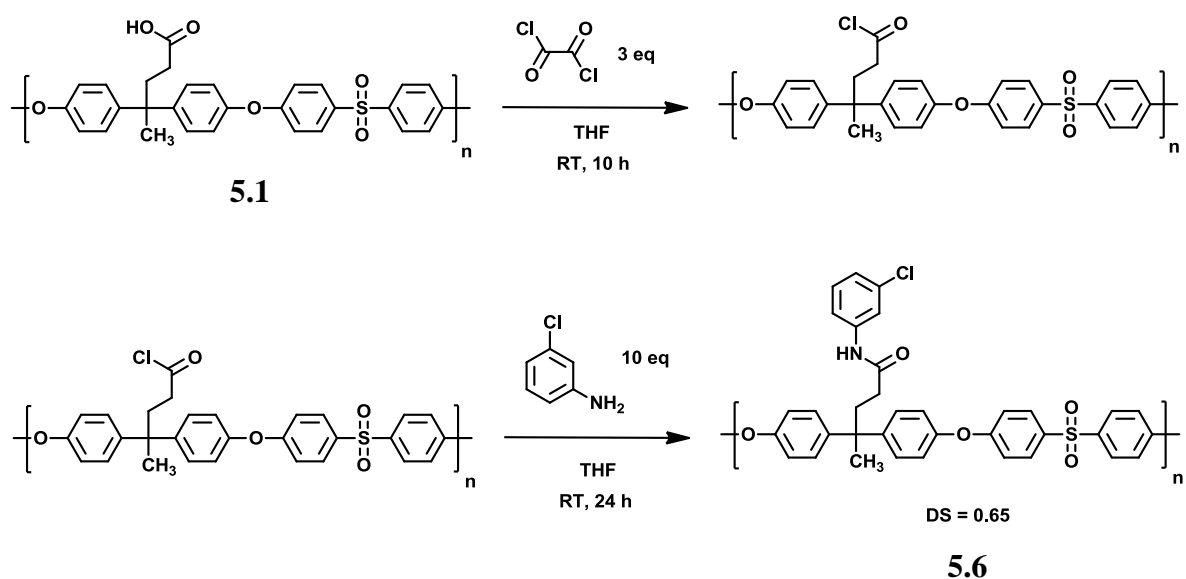
Another possible solution involves the maximum polymer chain length being controlled through varying the monomer content. As previously mentioned, a non-stoichiometric mix of starting monomers will result in a limited maximum polymer size, governed by the Carothers equation. As such, varying the amount of monomers used should set a maximum attainable polymer size and therefore if the polymerisation is run until completion then the polymer generated should be of this maximum size. This can also be achieved by addition of end-capped monomers; monomers which are only monofunctionalised rather than difunctionalised, resulting in a termination effect of the polymerisation under the same principles. Substituting a known amount of 4,4-bis(4'-hydroxyphenyl)pentanoic acid with 4-(4-hydroxyphenyl)-4-(4-methoxyphenyl)pentanoic acid **5.5** may achieve the desired results.<sup>17</sup>

**5.5**

Concurrently to performing these polymerisation reactions, we attempted to functionalise the produced polymers.

Ritter *et al.*<sup>10</sup> used oxalyl chloride to convert their carboxylic acid oligomers into the resultant acid chloride which subsequently reacted with various primary amines to form an amide functionalised PSF oligomer. We attempted to use this methodology to install 3-aminophenyl boronic neopentyl ester **5.7** onto PSF **2.37-1** and PSF **5.1** as well as 3-chloroaniline as a control.

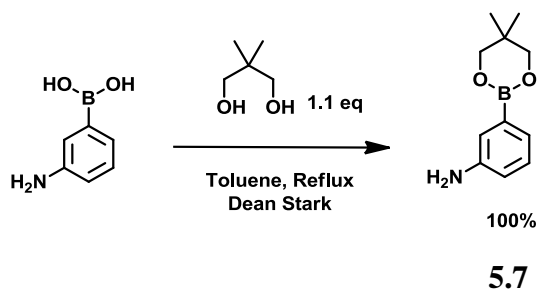
To a solution of PSF **5.1** dissolved in anhydrous THF was added 3 equivalents of oxalyl chloride whereupon the mixture was stirred for 10 hours at room temperature to form the acid chloride, which wasn't isolated. Following this excess oxalyl chloride was removed *en vacuo* and excess 3-chloroaniline was added, stirring at room temperature for 24 hours (Scheme 5.12).



Scheme 5.12

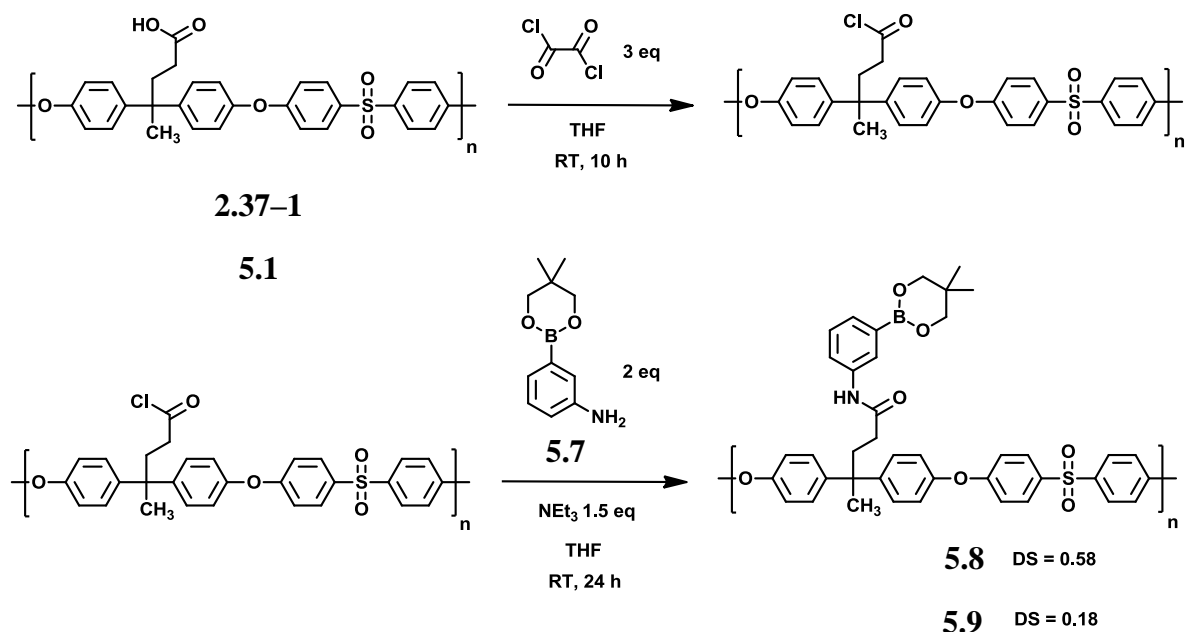
Due to overlap between the polymer back bone peaks and the aromatic peaks of the chloroaniline in the  $^1\text{H}$  NMR, the integration of the aromatic peaks could not be accurately measured. This meant that the yield was determined in relation to the integration of the amide peak at  $\delta 9.97$  ppm, though this value was within 10% of the partially observed aromatic peaks at  $\delta 7.76$  ppm and  $\delta 7.37$  ppm.

Neopentyl glycol protected 3-aminophenyl boronic acid **5.7** was chosen for its easy deprotection route and was synthesised *via* Dean Stark reflux in the same fashion as the aforementioned boronic acid protection reactions (Scheme 5.13).



Scheme 5.13

The reaction was conducted in the same manner as previously with **Scheme 5.12**. The 10 equivalents of 3-chloroaniline were replaced with 2 equivalents of the boronate ester **5.7** and 1.5 equivalents of  $\text{NEt}_3$ . Both PSF **2.37-1** and PSF **5.1** were used for this transformation (**Scheme 5.14**).

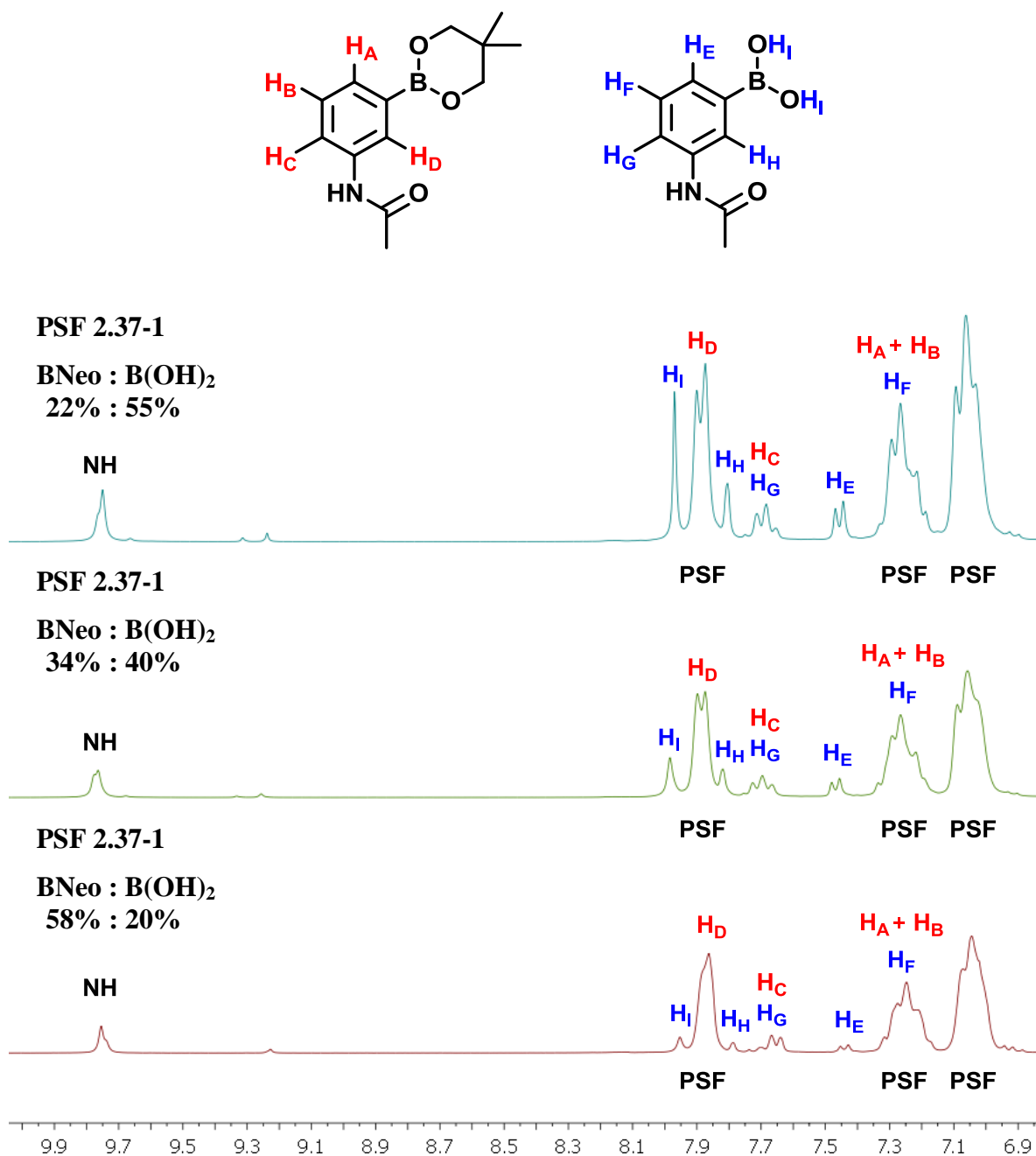


**Scheme 5.14**

The yields for the reaction were determined *via*  $^1\text{H}$  NMR, by comparing the two neopentyl glycol peaks at  $\delta 0.89$  ppm and  $\delta 3.71$  ppm with the polymer backbone methyl peak at  $\delta 1.62$  ppm. They were generally poor, with a DS of 0.58 being the best yield obtained after multiple attempts.

However, upon closer inspection of the spectra, the amide and appended aromatic signals did not integrate to each other or the neopentyl glycol which suggested that some of the boronate ester had been converted into the boronic acid, creating extra aromatic environments. When comparing the spectra of different yielding reactions it was noted that the peaks belonging to  $\text{H}_\text{E}$ ,  $\text{H}_\text{H}$  and  $\text{H}_\text{I}$  decreased in intensity in relation to an increase in neopentyl content, as denoted in **Figure 5.2**, suggesting that they belonged to the deprotected product. The  $\text{H}_\text{A}$ - $\text{H}_\text{D}$  protons belonging to the protected product are

unfortunately all overlapping with PSF backbone aromatic peaks so cannot be used to measure the level of deprotection directly.



**Figure 5.2:** Overlay of 300 MHz <sup>1</sup>H NMR spectra of PSF 2.37-1 at differing levels of deprotection.

However, the amount of deprotection can be elucidated by comparing the neopentyl peak integration with that belonging to  $H_E$  as it is generally free of overlap. The NH signal can also give a rough estimate to the total amount of amide present.

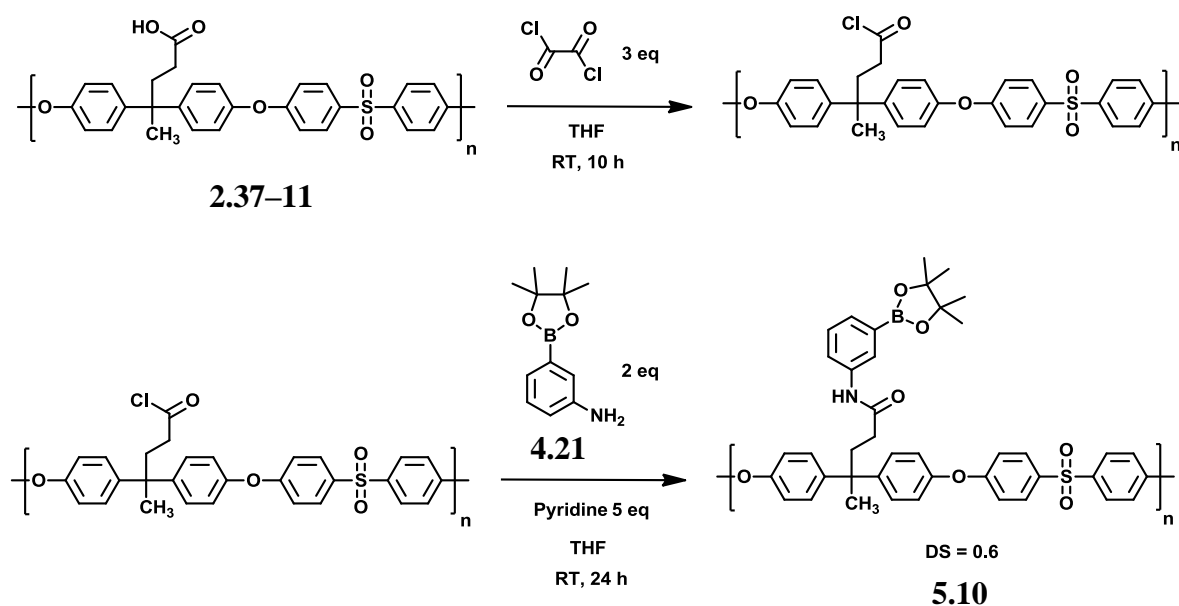
This deprotection is perhaps not unsurprising, as neopentyl glycol is a fairly labile protecting group. Whilst it was chosen for its ease of deprotection, it is clearly not robust enough to withstand the aqueous work up procedure, involving repeated washings and filtrations with water and EtOH. In addition, the by-product of the acid chloride formation is HCl which may accelerate the deprotection process despite the presence of  $NEt_3$ . The deprotection could potentially be limited by using an increased amount of base in the reaction as well minimising the amount of water in the workup, using anhydrous hexane as the precipitant.

Rather than try and optimise the neopentyl protected route, it was decided to switch to a less labile protecting group. We repeated the previous set of conditions using 3-aminophenyl pinacol boronate ester **4.21**, with pinacol being a robust enough protecting group to withstand thorough filtering and washing with water. In order to ensure there was no acid facilitated deprotection the  $NEt_3$  was substituted for 5 equivalents of pyridine.

Having consumed all of the available PSF **2.37-1** with the previously attempted synthesis, PSF **2.37-11** was used for the pinacol protected method. PSF **2.37-1** with its small  $M_w$  of 2600 contains a relatively high number of terminal hydroxyl groups per carboxylic acid, and this may be another reason for the poor yields, with the hydroxyls able to react with oxalyl chloride. PSF **2.37-11** on the other hand not only has properties very similar to Udel PSF, but with its  $M_w$  of 98700 has a very low amount of hydroxyl groups relative to the carboxylic acids and thus will not interfere with the reaction, potentially giving a superior yield.

Unfortunately, PSF **2.37-11** in fact caused the yield to be as poor as the neopentyl protected variant, giving only a DS of 0.6 (**Scheme 5.15**).





Scheme 5.15

This result was not due to deprotection, but rather a side effect of the polymers large size reducing the overall yield of the reaction. When attempting to remove excess oxalyl chloride from the mixture *en vacuo*, whilst PSF **2.37-1** encountered no difficulties, PSF **2.37-11** foamed and formed thick polymer films, trapping the solvent and preventing complete evaporation. In order to achieve complete removal of the oxalyl chloride the polymer required repeated solvations and evaporations, which is suspected to have resulted in quenching of a number of the acid chloride sites, resulting in a loss of yield. This problem is inherent of a property we desire of the polymer, thus it was clear a different approach would have to be undertaken.

Although peptide coupling of the amino boronate ester to the carboxylic acid is the obvious solution to this issue, it was decided that further optimisation of this route was potentially not the best direction for our research, considering the polymerisation itself was also far from optimised. With the difficulties both with the polymerisation process and the functionalisation stemming from the carboxylic acid group, changing the carboxylic acid monomer used to a less reactive functionalised monomer has the potential not only to deliver a superior polymer, but one which could be further modified in a cleaner fashion.

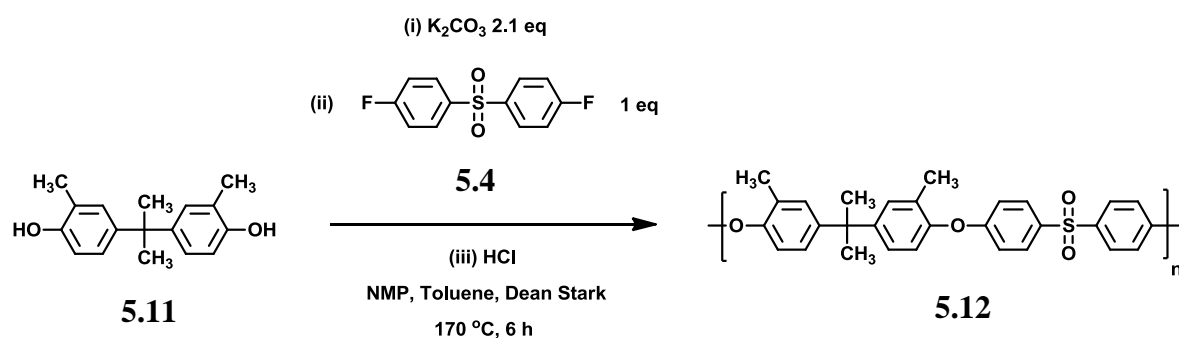
### 5.5 Polymerisation with Bisphenol C

With 4,4-bis(4'-hydroxyphenyl)pentanoic acid determined to be unsuitable for continued research we again searched for commercially available bisphenol A analogues. Whilst perhaps not an obvious functional monomer, Zhang *et al.*<sup>18</sup> used 2,2-bis(4-hydroxy-3-methyl-phenyl)propane, otherwise known as bisphenol C, alongside bis(4-fluorophenyl)sulfone to synthesise dimethylated PSF in a similar fashion to our previous experiment. As discussed in section 4.8, the benzyl position of methylated PSF is susceptible to radical bromination to generate a bromomethylated polymer, a highly desirable functionality.

It was hoped that as the dimethyl monomer contains no functionality with which to interfere with the polymerisation process that it would polymerise more uniformly, allowing us to produce a polymer with a consistent molecular weight. Once the dimethyl polymer is synthesised, subsequent functionalisations should be trivial.

We initially followed the polymerisation conditions set out by Zhang *et al.* Though milder than the semi-successful conditions we employed previously, it was believed that the cleaner polymerisation process would give a better polymer than equivalent conditions used with the carboxylic acid variant.

The dimethyl monomer **5.11** was stirred with 2 equivalents of  $K_2CO_3$  in NMP for 2 hours with toluene azeotroping water out of the mixture, following which the difluorophenyl sulfone was added and refluxed for 4 hours before the reaction was quenched with HCl (**Scheme 5.16**).



Scheme 5.16

The produced polymer is nearly identical to PSF **4.25** described in section **4.8**, which was developed concurrently to this line of research from brominated PSF **2.27**. There are however two not insignificant differences; the polymer synthesised from *n*-BuLi will contain minor amounts of unreacted aryl bromine and *ortho*-sulfone methyl groups whereas PSF **5.12** will be methylated to exactly 200% of the *ortho*-ether sites. PSF **5.12** will, however, have a variable size depending on the polymerisation process, whereas PSF **4.25** will be constant.

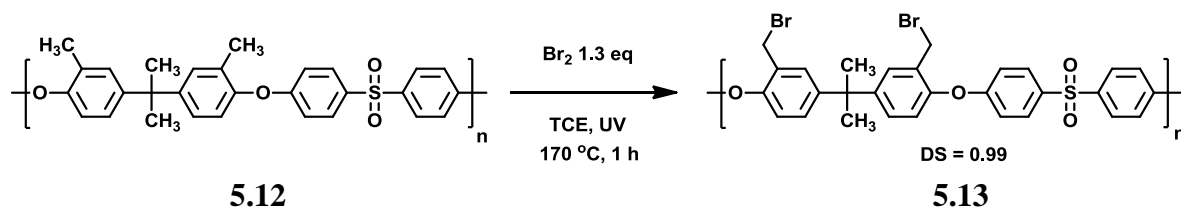
These first attempted conditions produced a polymer with disappointingly low  $M_w$  and  $M_n$ , though perhaps not surprising considering the low reaction time (Table 5.8).

| Polymer         | $M_n$ / Da | $M_w$ / Da | PD   |
|-----------------|------------|------------|------|
| PSF <b>5.12</b> | 8100       | 13250      | 1.63 |

Table 5.8: Properties of synthesised PSF **5.13**.

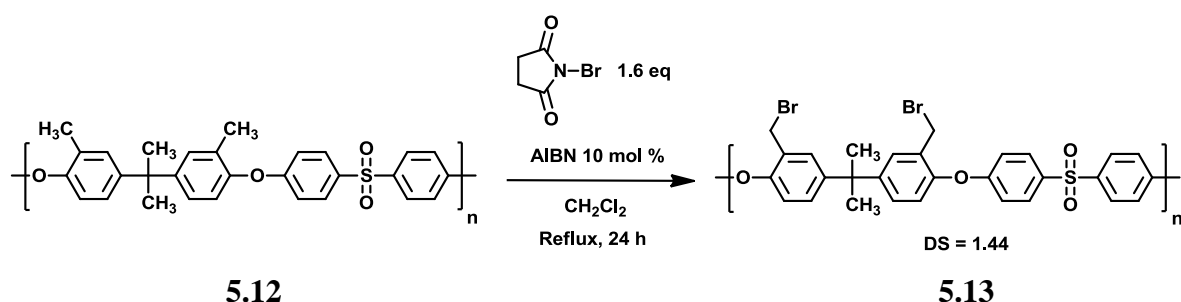
The produced polymer was subsequently subject to bromination conditions as described by Zhang *et al.*, whereupon a refluxing solution of PSF **5.13** in tetrachloroethane was exposed to 0.2 Å Long Wave radiation from a UV lamp. To this, 1.3 equivalents of  $\text{Br}_2$  were added

drop wise followed an additional hour of reflux and subsequent precipitation into methanol, brominating the polymer to a DS of 0.99 (**Scheme 5.17**).



Scheme 5.17

Whilst successful, the UV initiated method requires relatively harsh conditions in comparison to the NBS/AIBN mediated approach used in section 4.8 and when applied to PSF **5.12** they generated a polymer with a higher degree of bromination (**Scheme 5.18**).



Scheme 5.18

At this point in our research, though this method of synthesising bromomethylated PSF had been successful, with a large amount of scope for optimising the polymerisation process, the simultaneously developed *n*-BuLi mediated bromomethylation reaction produces comparable levels of functionalisation, but with consistent polymer properties and a shorter reaction time. It was therefore deemed that this approach was unnecessary when a superior one existed and as such this line of research was stopped.

## 5.6 Conclusion and Future Work

Due to the overall difficulty in functionalising PSF, it was suspected that polymerising functional monomers may provide an easier route to the desired modified polymer, especially with the commercial availability of a variety of functional analogues of bisphenol A and bis(4-fluorophenyl)sulfone.

The polymerisation of 4,4-bis(4'-hydroxyphenyl)pentanoic acid in place of bisphenol A provided a PSF functionalised by a tethered carboxylic acid chain, ideal as a linker and a tether for a subsequently appended carrier. Whilst the literature precedence for the polymerisation produced small oligomeric molecules, we have shown the ability to create much larger high molecular weight polymeric carboxylated PSFs, a vast improvement. These polymers were then successfully appended with boronic acids, though the heavier polymers proved difficult to obtain quantitative yields. Unfortunately, the polymerisation process failed to give consistent sized polymers, a trait necessary to create hollow fibres with, though it is theorised that use of a mechanical overhead stirrer would give a more regular polymer.

The polymerisation of bisphenol C to create dimethylated PSF was also attempted, with the produced polymer easily brominated to yield a highly functionalised bromomethylated polymer.

The appeal of these methodologies is that the polymerisation processes are potentially easier to achieve than the equivalent functionalisation of PSF. However, with the perfection of *n*-BuLi mediated functionalisation techniques, modification of PSF is a simple and quantitative task, and thus overall a superior technique than the polymerisations.

### 5.7 References

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## Chapter 6 : Experimental

### 6.1 General Procedures

Commercially available reagents and solvents were obtained from Sigma-Aldrich, Fisher Scientific, Frontier Scientific, Alfa Aesar, TCI and Acros Organics and used without further purification unless otherwise stated.

All air-sensitive reactions were carried out with anhydrous solvent under a dry nitrogen atmosphere using a standard Schlenk line. DCM, THF, methanol and hexane were dried and degassed under an argon atmosphere over activated alumina columns using an Innovative Technology Solvent Purification System (SPS) prior to use in air sensitive reactions. DMSO was heated over NaOH and distilled over 4 Å molecular sieves under a nitrogen atmosphere.

NMR spectra were recorded on Bruker AV300 or AVANCE 400 spectrometers at 298 K. Chemical shifts ( $\delta$ ) are expressed in parts per million (ppm).  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were referenced internally to residual protio-solvent. All  $^{13}\text{C}$  NMR spectra were run as PENDANT experiments for polymer structural elucidation. Assignments were supported by  $^{11}\text{B}$  NMR,  $^{19}\text{F}$  NMR and homo- and hetero-nuclear, one- and two-dimensional experiments as appropriate. The multiplicities of the spectroscopic data are presented in the following manner: singlet (s), broad singlet (br. s), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), triplet (t), quartet (q), septet (sept) and multiplet (m). Coupling constants ( $J$ ) are expressed in Hertz (Hz). Polymers produced where DS  $\neq$  1.0 or 2.0 are reported as a mixture, with the relevant peaks referenced as starting material (SM) and product (Prod). Peaks split by differing mono- and disubstitution effects are reported as monosubstitution (Mono) and disubstitution (Di).

Analytical thin layer chromatography (TLC) was performed using commercially available aluminium backed plates coated with Merk Kieselgel 60 0.20 mm, (ALUGRAM® sil G/UV254) and visualised under ultra-violet light (254 nm), or by staining with potassium permanganate, ninhydrin, vanillin, cobalt chloride or curcumin solution. Flash column chromatography was carried out using Merck Kieselgel 60 H silica gel.

Infrared spectra were recorded on a Perkin Elmer (Spectrum 100) FT-IR spectrometer, over the range 4000-600  $\text{cm}^{-1}$  and averaged over 32 scans with internal calibration.

Gel Permeation Chromatography (GPC) analyses were performed on a Polymer Laboratories PL-GPC 50 integrated system using a PLgel 5  $\mu\text{m}$  MIXED-D300x 7.5 mm column at 35 °C, THF solvent (flow rate, 1.0 mL/min). The polydispersity index (PDI) was determined from  $M_w/M_n$ , where  $M_n$  is the number average molecular weight and  $M_w$  the weight average molecular weight. The polymers were referenced to 11 narrow molecular weight polystyrene standards with a range of  $M_w$  615 – 568000 Da.

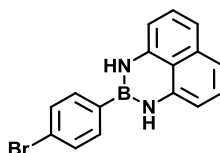


## 6.2 Protection of Boronic Acids

### 6.2.1 General Procedure for the Protection of Boronic Acids

Boronic acid (1 eq) was dissolved in toluene and protecting group (1.1 eq) added. Water was removed by azeotropic distillation by the Dean-Stark method overnight. The reaction was filtered through a plug of silica, and the filtrate concentrated *in vacuo* to afford the desired boron compound.

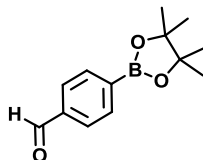
### 6.2.2 2-(4-bromophenyl)-2,3-dihydro-1H-naphtho[1,8-de][1,3,2]diazaborinine (3.11)



Following the general procedure 4-bromophenylboronic acid (1 g, 4.97 mmol) was reacted with 1,8-diaminonaphthalene (0.87 g, 5.47 mmol) in toluene (20 mL) to give the title compound in quantitative yield (1.6 g).

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ); 5.97 (2H, br. s, *NH*), 6.42 (2H, dd,  $J = 7.1, 1.0$  Hz, *ArH*), 7.08 (2H, dd,  $J = 8.3, 1.0$  Hz, *ArH*), 7.16 (2H, dd,  $J = 8.2, 7.2$  Hz, *ArH*), 7.50 (2H, d,  $J = 8.3$  Hz, *ArH*), 7.58 (2H, d,  $J = 8.3$  Hz, *ArH*);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ); 106.6, 118.5, 120.6, 125.3, 128.0, 131.9, 133.4, 136.7, 141.2 (C-B not observed);  $\delta_{\text{B}}$  (96 MHz;  $\text{CDCl}_3$ ); 29.9.

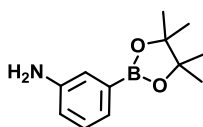
All data in accordance with literature values <sup>1</sup>

**6.2.3 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (4.13)**

Following the general procedure 4-formylphenylboronic acid (0.5 g, 3.3 mmol) was reacted with pinacol (0.46 g, 3.63 mmol) in toluene (20 mL) to give the title compound in quantitative yield (0.77 g).

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ); 1.36 (12H, s,  $\text{CH}_3$ ), 7.86 (2H, d,  $J = 8.2$  Hz,  $\text{ArH}$ ), 7.96 (2H, d,  $J = 8.1$  Hz,  $\text{ArH}$ ), 10.04 (1H, s,  $\text{CHO}$ );  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ); 25.3, 84.7, 129.1, 135.6, 138.5, 193.0 (C-B not observed);  $\delta_{\text{B}}$  (96 MHz;  $\text{CDCl}_3$ ); 31.3.

All data in accordance with literature values<sup>2</sup>

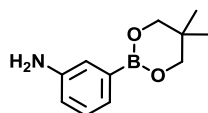
**6.2.4 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (4.21)**

Following the general procedure 3-aminophenylboronic acid monohydrate (1 g, 6.45 mmol) was reacted with pinacol (0.84 g, 7.1 mmol) in toluene (20 mL) to give the title compound in quantitative yield (1.41 g).

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ); 1.34 (12H, s,  $\text{CH}_3$ ), 3.60 (2H, br. s,  $\text{NH}_2$ ), 6.79 (1H, ddd,  $J = 7.5$ , 2.6, 1.5 Hz,  $\text{ArH}$ ), 7.13-7.25 (3H, m,  $\text{ArH}$ );  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ); 25.28, 84.12, 118.51, 121.60, 125.42, 129.17, 146.09 (C-B not observed);  $\delta_{\text{B}}$  (96 MHz;  $\text{CDCl}_3$ ); 31.6

All data in accordance with literature values<sup>3,4</sup>

### 6.2.5 3-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)aniline (5.7)

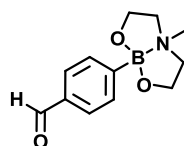


Following the general procedure 3-aminophenylboronic acid monohydrate (0.5 g, 3.2 mmol) was reacted with 2,2-dimethylpropane-1,3-diol (0.37 g, 3.52 mmol) in toluene (20 mL) to give the title compound in quantitative yield (0.66 g).

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ); 1.30 (6H, s,  $\text{CH}_3$ ), 3.55 (2H, br. s,  $\text{NH}_2$ ), 3.75 (4H, s,  $\text{CH}_2$ ), 6.78 (1H, ddd,  $J = 7.5, 2.6, 1.5$  Hz,  $\text{ArH}$ ), 7.11-7.25 (3H, m,  $\text{ArH}$ );  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ); 22.3, 32.3, 72.8, 118.0, 120.8, 124.6, 129.0, 146.1 (C-B not observed);  $\delta_{\text{B}}$  (96 MHz;  $\text{CDCl}_3$ ); 27.5

All data in accordance with literature values<sup>5</sup>

### 6.2.6 4-(6-methyl-1,3,6,2-dioxazaborocan-2-yl)benzaldehyde (4.16)

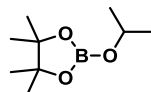


4-formylphenylboronic acid (0.5 g, 3.3 mmol) was dissolved in THF (5 mL) and *N*-methyl diethanolamine (0.44 g, 3.7 mmol) added. The reaction was stirred at room temperature for 30 minutes followed by addition of water (30 mL) and extraction of the aqueous layer with

$\text{CHCl}_3$  (3 x 20 mL). The combined organic extracts were dried over  $\text{Na}_2\text{SO}_4$  and concentrated *in vacuo* to give the title compound in quantitative yield (0.77 g).

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ); 2.26 (3H, s,  $\text{CH}_3$ ), 2.92-3.02 (2H, m,  $\text{CH}_2$ ), 3.13-3.21 (2H, m,  $\text{CH}_2$ ), 4.03-4.23 (4H, m,  $\text{CH}_2$ ), 7.74 (4H, s, ArH), 9.93 (1H, s, CHO);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ); 48.1, 62.2, 62.9, 129.2, 134.1, 136.4, 193.6 (C-B not observed);  $\delta_{\text{B}}$  (96 MHz;  $\text{CDCl}_3$ ); 12.7

### 6.2.7 Isopropyl Pinacol Borate (4.3)

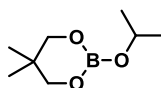


Equimolar amounts of  $\text{B}(\text{O}^i\text{Pr})_3$  (20 g, 106 mmol) and pinacol (10.9 g, 106 mmol) were dissolved in hexane (150 mL), whereupon they were heated at 60 °C. As the reaction progresses, isopropanol is produced and continuously azeotropically distilled with hexane out of the reaction mixture. Once the reaction is complete and all the solvent has been removed, the product is purified by distilling it into a fresh reaction vessel at 10 torr to separate it from any unreacted pinacol and giving the title compound at 90% yield (17.75 g).

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ); 1.16 (6H, d,  $J$  = 6.1 Hz,  $\text{CH}_3$ ), 1.21 (12H, s,  $\text{CH}_3$ ), 4.29 (1H, sept,  $J$  = 6.1 Hz, CH);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ); 24.7, 24.9, 67.7, 82.8;  $\delta_{\text{B}}$  (96 MHz;  $\text{CDCl}_3$ ); 22.6

All data in accordance with literature values<sup>6</sup>

### 6.2.8 2-Isopropoxy-5,5-dimethyldioxaborinane (4.4)

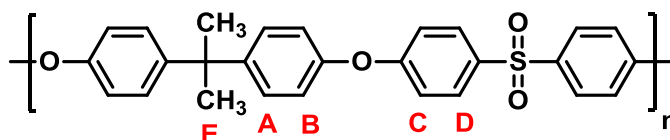


Equimolar amounts of  $\text{B}(\text{O}^i\text{Pr})_3$  (20 g, 106 mmol) and 2,2-propane-1,3-diol (11.04 g, 106 mmol) were dissolved in hexane (150 mL), whereupon they were heated at 60 °C. As the reaction progresses, isopropanol is produced and continuously azeotropically distilled with hexane out of the reaction mixture. Once the reaction is complete and all the solvent has been removed, the product is purified by distilling it into a fresh reaction vessel at 10 torr to separate it from any unreacted 2,2-propane-1,3-diol and giving the title compound at 85% yield (15.5 g).

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ); 0.95 (6H, s,  $\text{CH}_3$ ), 1.57 (6H, d,  $J = 6.1$  Hz,  $\text{CH}_3$ ), 3.62 (4H, s,  $\text{CH}_3$ ), 4.33 (1H, sept,  $J = 6.1$  Hz,  $\text{CH}$ );  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ); 21.6, 24.4, 32.0, 65.24, 72.93;  $\delta_{\text{B}}$  (96 MHz;  $\text{CDCl}_3$ ); 20.6

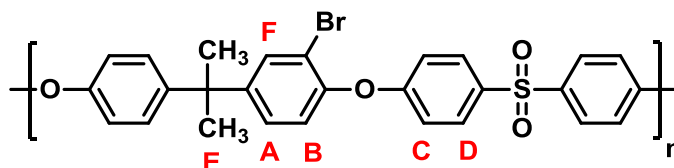
### 6.3 Electrophilic Aromatic Substitution

#### 6.3.0 PSF (2.20)



$\nu_{\text{max}}$  (neat)/ $\text{cm}^{-1}$ ; 3070, 2970 (C-H), 1585, 1505, 1490 (C=C);  $\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ); 1.69 ( $\text{H}_{\text{E}}$ , s), 6.93 ( $\text{H}_{\text{B}}$ , d,  $J = 8.8$  Hz), 7.00 ( $\text{H}_{\text{C}}$ , d,  $J = 8.9$  Hz), 7.24 ( $\text{H}_{\text{A}}$ , d,  $J = 8.8$  Hz), 7.84 ( $\text{H}_{\text{D}}$ , d,  $J = 8.9$  Hz);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ); 31.4, 42.8, 118.1, 120.2, 128.8, 130.1, 135.8, 147.6, 153.2, 162.4

### 6.3.1 Brominated PSF (2.27)

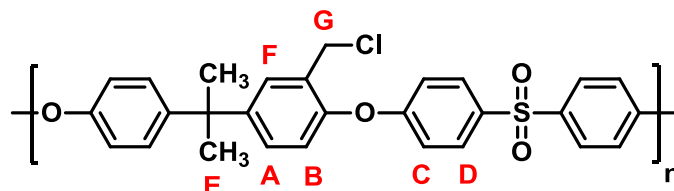


To a stirred solution of PSF **2.20** (50 g, 0.113 mol) in  $\text{CHCl}_3$  (250 mL) was added  $\text{Br}_2$  (16 mL, 0.311 mol), releasing a large amount of  $\text{HBr}$  gas. After 24 hours the mixture was poured slowly into 2 L of stirred MeOH. The formed lump precipitate was stirred for 1 hour to leach out residual bromine. It was then filtered, redissolved and precipitated a further 2 times before finally being filtered and washed with water. The product was dried in a vacuum oven at 40 °C over 2 days to produce a white polymer brominated with a degree of substitution of 2.0.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ); 1.69 ( $\text{H}_{\text{E}}$ , s), 6.96 ( $\text{H}_{\text{C}}$ , d,  $J = 8.8$  Hz), 6.96 ( $\text{H}_{\text{B}}$ , d,  $J = 8.5$  Hz), 7.15 ( $\text{H}_{\text{A}}$ , dd,  $J = 8.5, 2.2$  Hz), 7.51 ( $\text{H}_{\text{F}}$ , d,  $J = 2.2$  Hz), 7.86 ( $\text{H}_{\text{D}}$ , d,  $J = 8.9$  Hz);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ); 31.1, 43.0, 116.2, 117.3, 122.5, 128.1, 130.3, 132.6, 136.1, 149.0, 150.1, 161.5

All data in accordance with literature values<sup>7</sup>

### 6.3.2 Chloromethylated PSF (3.1) DS = 0.38

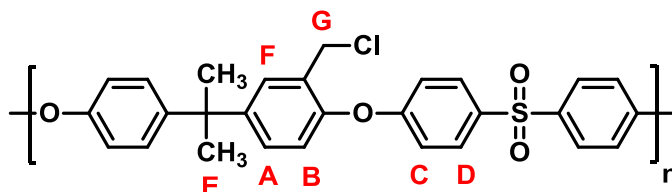


To a stirred solution of PSF **2.20** (2.65 g, 5.99 mmol) dissolved in anhydrous DCM (140 mL) and heated to 50 °C and under a nitrogen atmosphere was added paraformaldehyde

(0.531 g, 17.7 mmol), TMSCl (2.23 mL, 17.7 mmol) and 2M SnCl<sub>4</sub> (0.6 mL, 1.198 mmol). After 28 hours the mixture was poured slowly into 1 L of stirred MeOH, with the lump precipitate formed filtered, redissolved and precipitated 2 more times before finally being filtered and washed with water and then dried in a vacuum oven at 40 °C over 2 days, producing a white polymer chloromethylated with a degree of substitution of 0.38.

$\delta_H$  (300 MHz; CDCl<sub>3</sub>): 1.69 (H<sub>E</sub>, s, SM + Prod), 4.53 (H<sub>G</sub>, s, Prod), 6.83 (H<sub>B</sub>, d,  $J$  = 8.6 Hz, Prod), 6.93 (H<sub>B</sub>, d,  $J$  = 8.7 Hz, SM), 7.0 (H<sub>C</sub>, d,  $J$  = 8.8 Hz, SM + Prod), 7.16 (H<sub>A</sub>, dd,  $J$  = 8.6, 2.2 Hz, Prod), 7.24 (H<sub>A</sub>, d,  $J$  = 8.7 Hz, SM), 7.36 (H<sub>F</sub>, d,  $J$  = 2.3 Hz, Prod), 7.84 (H<sub>D</sub>, d,  $J$  = 8.8 Hz, SM + Prod);  $\delta_C$  (75.5 MHz; CDCl<sub>3</sub>): 31.5, 41.5, 42.9, 118.2, 118.3, 120.3, 120.4, 128.9, 129.5, 129.9, 130.2, 130.3, 135.9, 147.7, 153.3, 162.5

### 6.3.3 Chloromethylated PSF (3.1) DS = 0.58

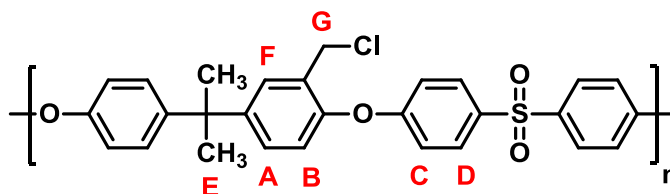


To a stirred solution of PSF **2.20** (5.3 g, 11.9 mmol) dissolved in anhydrous DCM (200 mL) and heated to 50 °C under a nitrogen atmosphere was added paraformaldehyde (3.57 g, 119 mmol), TMSCl (15 mL, 119 mmol) and 1M SnCl<sub>4</sub> (1.19 mL, 1 mmol). After 72 hours the mixture was poured slowly into 1 L of stirred MeOH, with the lump precipitate formed filtered, redissolved and precipitated 2 more times before finally being filtered and washed with water and then dried in a vacuum oven at 40 °C over 2 days, producing a white polymer chloromethylated with a degree of substitution of 0.58.

$\delta_H$  (300 MHz; CDCl<sub>3</sub>): 1.7 (H<sub>E</sub>, s, SM + Prod), 4.54 (H<sub>G</sub>, s, Prod), 6.84 (H<sub>B</sub>, d,  $J$  = 8.8 Hz, Prod), 6.94 (H<sub>B</sub>, d,  $J$  = 8.8 Hz, SM), 7.0 (H<sub>C</sub>, d,  $J$  = 8.9 Hz, SM + Prod), 7.14-7.20 (H<sub>A</sub>, m, Prod), 7.25 (H<sub>A</sub>, m, SM), 7.36-7.38 (H<sub>F</sub>, m, Prod), 7.85 (H<sub>D</sub>, d,  $J$  = 8.9 Hz, SM + Prod);  $\delta_C$

(75.5 MHz; CDCl<sub>3</sub>); 31.4, 41.4, 42.8, 118.1, 118.2, 120.2, 120.5, 129.4, 129.9, 130.1, 135.8, 147.6, 153.2, 162.4

#### 6.3.4 Chloromethylated PSF (3.1) DS = 1.13

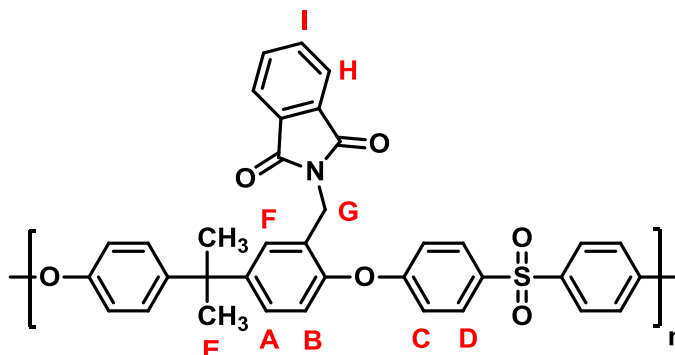


To a stirred solution of PSF **2.20** (1 g, 2.2 mmol) dissolved in anhydrous DCM (10 mL) a mixture of MOMCl (1.89 mL, 25 mmol) and ZnCl<sub>2</sub> (0.075 g, 0.55 mmol) was added dropwise whereupon the reaction was heated to 40 °C. After 5 hours the mixture was poured slowly into 1 L of stirred MeOH, with the lump precipitate formed filtered, redissolved and precipitated 2 more times before finally being filtered and washed with water and then dried in a vacuum oven at 40 °C over 2 days, producing a white polymer chloromethylated with a degree of substitution of 1.13.

$\delta_H$  (300 MHz; CDCl<sub>3</sub>): 1.70 (H<sub>E</sub>, s, SM + Prod), 4.54 (H<sub>G</sub>, s, Prod), 6.85 (H<sub>B</sub>, dt,  $J = 8.6$ , 1.8 Hz, Prod), 6.92-6.98 (H<sub>B</sub>, m, SM), 6.98-7.06 (H<sub>C</sub>, m, SM + Prod), 7.17 (H<sub>A</sub>, dt,  $J = 8.6$ , 2.0 Hz, Prod), 7.25 (H<sub>A</sub>, d,  $J = 8.8$  Hz, SM), 7.37 (H<sub>F</sub>, d,  $J = 2.3$  Hz, Prod), 7.82-7.91 (H<sub>D</sub>, m, SM + Prod)



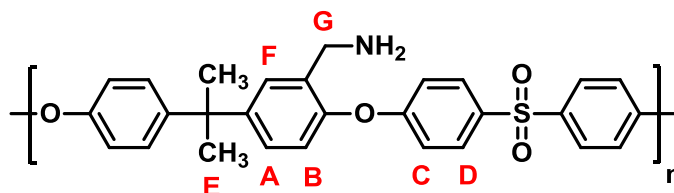
## 6.3.5 Phthalimided PSF (3.12) DS = 1.10



To a solution of PSF **2.20** (5 g, 11.2 mmol) dissolved in anhydrous DCM (50 mL) was added *N*-chloromethylphthalimide (5.48g, 28 mmol) and FeCl<sub>3</sub> (0.1g, 0.62 mmol) whereupon the reaction was heated to 40 °C. After 24 hours the mixture was poured slowly into 1 L of stirred MeOH, with the lump precipitate formed filtered, redissolved and precipitated 2 more times before finally being filtered and washed with water and then dried in a vacuum oven at 40 °C over 2 days, producing a white polymer phthalimided with a degree of substitution of 1.10.

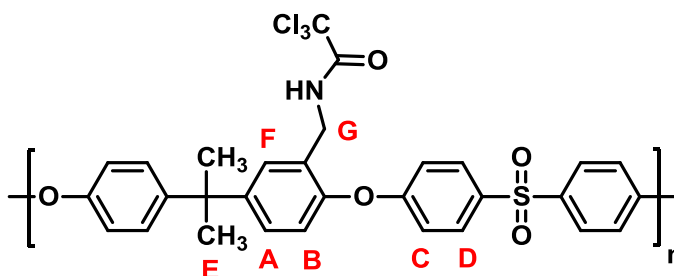
$\delta_H$  (300 MHz; CDCl<sub>3</sub>): 1.68 (H<sub>E</sub>, s, SM + Prod), 4.75 (H<sub>G</sub>, s, Prod, Major Rotamer), 4.78 (H<sub>G</sub>, s, Prod, Minor Rotamer) 6.77-6.85 (H<sub>B</sub>, m, Prod), 6.86-6.97 (H<sub>C</sub>, m, SM + Prod), 7.00 (H<sub>B</sub>, d,  $J$  = 8.0 Hz, SM), 7.10-7.18 (H<sub>A</sub>, m, Prod), 7.19-7.28 (H<sub>A</sub>, m, SM), 7.31 (H<sub>F</sub>, dd,  $J$  = 6.9, 2.3 Hz, Prod), 7.59-7.88 (H<sub>D</sub> + H<sub>H</sub> + H<sub>I</sub>, m, SM + Prod);  $\delta_C$  (75.5 MHz; CDCl<sub>3</sub>): 31.4, 37.7, 42.8, 117.5, 118.1, 120.2, 120.9, 123.5, 127.9, 128.3, 128.9, 130.0, 132.1, 134.5, 147.5, 150.7, 153.2, 162.3, 168.0

## 6.3.6 Aminomethylated PSF (3.13)



A solution of phthalimidated PSF **3.12**  $DS = 0.78$  (0.27 g, 0.46 mmol) and 50-60% hydrazine hydrate solution (0.073 mL, 1.4 mmol) in 8:2 DCM:EtOH (4 mL: 1mL) was refluxed for 12 hours before being poured into 50 mL of stirred EtOH and the precipitate filtered, washed with water and dried to give the title compound with full deprotection.

$\delta_H$  (300 MHz;  $CDCl_3$ ); 1.71 ( $H_E$ , s, SM + Prod), 3.73 ( $H_G$ , s, Prod), 6.84 ( $H_B$ , d,  $J = 8.4$  Hz, Prod), 6.94 ( $H_B$ , d,  $J = 8.6$  Hz, SM), 7.01 ( $H_C$ , d,  $J = 8.9$  Hz, SM + Prod), 7.11 ( $H_A$ , dd,  $J = 8.4, 2.2$  Hz, Prod), 7.25 ( $H_A$ , d,  $J = 8.6$  Hz, SM), 7.29-7.33 ( $H_F$ , m, Prod), 7.85 ( $H_D$ , d,  $J = 8.9$  Hz, SM + Prod);  $\delta_C$  (75.5 MHz;  $CDCl_3$ ); 31.4, 42.3, 42.9, 117.4, 118.1, 120.2, 120.7, 128.1, 128.8, 130.1, 135.8, 147.5, 148.2, 150.8, 153.2, 162.3

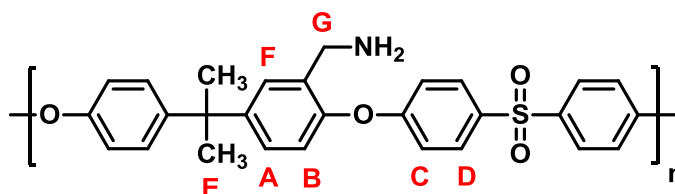
6.3.7 Trichloroacetamidated PSF (3.14)  $DS = 0.90$ 

To a pressure tube was added PSF **2.20** (1 g, 2.26 mmol), trichloroacetamide (1.095 g, 6.78 mmol), paraformaldehyde (0.2 g, 6.78 mmol), 48%  $BF_3 \cdot Et_2O$  (0.32 mL, 2.26 mmol) and

anhydrous DCM (8 mL). After refluxing for 12 hours the mixture was poured into 500 mL of stirred MeOH, filtered, washed with water and dried in a vacuum oven at 40 °C over 2 days to give the title compound with a degree of substitution of 0.90.

$\nu_{\max}$  (neat)/ $\text{cm}^{-1}$ ; 2970 (C-H), 1715 (C=O), 1585, 1505, 1490 (C=C);  $\delta_{\text{H}}$  (300 MHz; DMSO- $\text{d}_6$ ); 1.60 ( $\text{H}_{\text{E}}$ , s, SM + Prod), 4.26 ( $\text{H}_{\text{G}}$ , br. s, Prod), 6.85-7.3 ( $\text{H}_{\text{A}}$  +  $\text{H}_{\text{B}}$  +  $\text{H}_{\text{C}}$  +  $\text{H}_{\text{F}}$ , m, SM + Prod), 7.87 ( $\text{H}_{\text{D}}$ , br. s., SM + Prod), 9.36 (NH, br. s, Prod);  $\delta_{\text{C}}$  (75.5 MHz; DMSO- $\text{d}_6$ ); 30.9, 42.4, 93.0, 117.7, 118.1, 120.2, 127.3, 128.7, 129.5, 130.1, 135.5, 147.1, 152.6, 161.7, 163.1

### 6.3.8 Aminomethylated PSF (3.13)



To a stirred solution of trichloroacetamidated PSF **3.14** **DS** = **0.90** (1.16 g, 1.96 mmol) in DMSO (15 mL) was added  $\text{Cs}_2\text{CO}_3$  (1.92 g, 5.88 mmol) and the mixture heated at 100 °C. After 18 hours excess  $\text{NaHCO}_3$  solution was added and the mixture was precipitated into 500 mL of stirred EtOH, filtered, washed with water and dried in a vacuum oven at 40 °C over 2 days to give the title compound with full deprotection.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ); 1.71 ( $\text{H}_{\text{E}}$ , s, SM + Prod), 3.73 ( $\text{H}_{\text{G}}$ , s, Prod), 6.84 ( $\text{H}_{\text{B}}$ , d,  $J$  = 8.4 Hz, Prod), 6.94 ( $\text{H}_{\text{B}}$ , d,  $J$  = 8.6, SM), 7.01 ( $\text{H}_{\text{C}}$ , d,  $J$  = 8.9, SM + Prod), 7.11 ( $\text{H}_{\text{A}}$ , dd,  $J$  = 8.4, 2.2 Hz, Prod), 7.25 ( $\text{H}_{\text{A}}$ , d,  $J$  = 8.6 Hz, SM), 7.29-7.33 ( $\text{H}_{\text{F}}$ , m, Prod), 7.85 ( $\text{H}_{\text{D}}$ , d,  $J$  = 9.0 Hz, SM + Prod);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ); 31.4, 42.3, 42.9, 117.4, 118.1, 120.2, 120.7, 128.1, 128.8, 130.1, 135.8, 147.5, 148.2, 150.8, 153.2, 162.3

## 6.4 Lithiation

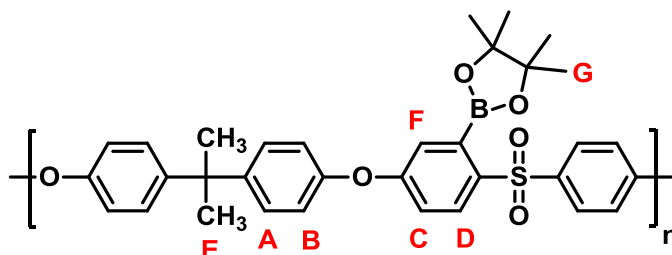
### 6.4.1 General Method of *Ortho*-Sulfone Lithiation

A stirred solution of PSF **2.20** in anhydrous THF is cooled to -78 °C (dry ice/acetone) under a N<sub>2</sub> atmosphere. *n*-BuLi (Xeq) was added drop wise *via* a syringe pump at a rate of 30 mL/h to generate *ortho*-sulfone lithiated PSF in quantitative yield. After 30 minutes excess electrophile is added in one portion and the reaction stirred for 3 hours and then allowed to warm to room temperature overnight. Upon quenching with acid, water or EtOH the mixture is poured into a large quantity of stirred precipitant, filtered, redissolved and precipitated 2 more times before finally being filtered and washed with water and then dried in a vacuum oven at 40 °C over 2 days to give the desired polymer in near quantitative yields.

### 6.4.2 General Method of *Ortho*-Ether Lithiation

A stirred solution of PSF **2.27** in anhydrous THF was cooled to -78 °C (dry ice/acetone) under a N<sub>2</sub> atmosphere. *n*-BuLi (Xeq) was added drop wise *via* a syringe pump at a rate of 30 mL/h to generate *ortho*-ether lithiated PSF as the major product with minor amounts of *ortho*-sulfone lithiated PSF produced. After 30 minutes excess electrophile is added in one portion and the reaction stirred for 3 hours and then allowed to warm to room temperature overnight. Upon quenching with acid or EtOH the mixture is poured into a large quantity of stirred precipitant, filtered, redissolved and precipitated 2 more times before finally being filtered and washed with water and then dried in a vacuum oven at 40 °C over 2 days to give the desired polymer in near quantitative yields.

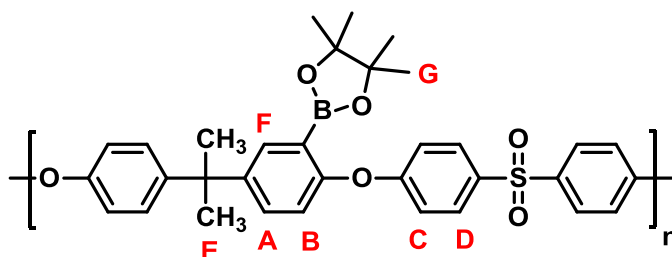
### 6.4.3 *Ortho*-sulfone Pinacol Borate PSF (3.10) DS = 1.50



Following the general method of *ortho*-sulfone lithiation, PSF **2.20** (1 g, 2.26 mmol) was lithiated with 2M *n*-BuLi (1.8 mL, 3.36 mmol) in anhydrous THF (25 mL) and quenched with excess isopropyl pinacol borate **4.3** (2 mL, 10 mmol) followed by water before precipitating into EtOH to give the title compound with a degree of substitution of 1.50.

$\delta_H$  (300 MHz;  $CDCl_3$ ); 1.24 ( $H_G$ , s, Prod, Major Rotamer), 1.27 ( $H_G$ , s, Prod, Minor Rotamer), 1.41 ( $H_G$ , s, Prod), 1.69 ( $H_E$ , s, SM + Prod), 6.86-6.96 ( $H_B$ , m, SM + Prod), 6.96-7.08 ( $H_C$ , m, SM + Prod, Mono and Di), 7.15-7.27 ( $H_A + H_F$ , m, SM + Prod), 7.78 ( $H_D$ , d,  $J = 8.8$  Hz, Prod, Mono), 7.85 ( $H_D$ , d,  $J = 8.8$  Hz, SM), 8.01 ( $H_D$ , d,  $J = 8.8$  Hz, Prod, Mono), 8.13 ( $H_D$ , d,  $J = 8.8$  Hz, Prod, Di);  $\delta_C$  (75.5 MHz;  $CDCl_3$ ); 25.3, 31.4, 42.8, 85.3, 118.0, 118.7, 120.2, 122.3, 128.8, 130.1, 130.5, 130.9, 135.9, 138.7, 147.6, 153.2, 161.4, 162.1, 162.4;  $\delta_B$  (96 MHz;  $CDCl_3$ ); No peak. Positive with curcumin.

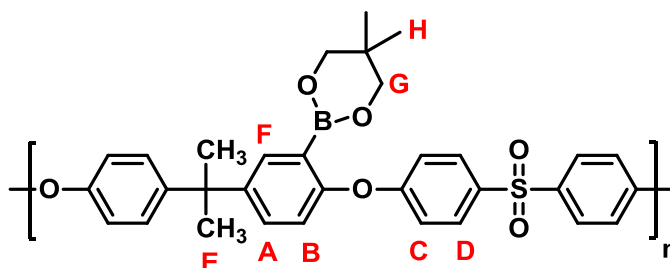
### 6.4.4 *Ortho*-ether Pinacol Borate PSF (3.17) DS = 0.50



Following the general method of *ortho*-ether lithiation, brominated PSF **2.27** **DS** = **0.80** (1 g, 1.98 mmol) was lithiated with 2M *n*-BuLi (0.64 mL, 1.28 mmol) in anhydrous THF (25 mL) and quenched with excess isopropyl pinacol borate **4.3** (3 mL, 1.52 mmol) followed by water before precipitating into EtOH to give the title compound with a degree of substitution of 0.50 as a 4:1 mixture of *ortho*-ether and *ortho*-sulfone product.

$\delta_H$  (300 MHz;  $CDCl_3$ ); 0.97-1.06 ( $H_G$ , m, Prod, *ortho*-ether), 1.22 ( $H_G$ , s, Prod, Rotamer), 1.25 ( $H_G$ , s, Prod, Rotamer), 1.41 ( $H_G$ , s, Prod, *ortho*-sulfone), 1.68 ( $H_E$ , s, SM + Prod, *ortho*-sulfone), 1.71 ( $H_E$ , s, Prod, *ortho*-ether), 6.80-7.05 ( $H_C$  +  $H_B$ , m, SM + Prod, *ortho*-ether + *ortho*-sulfone), 7.16-7.29 ( $H_A$ , m, SM + Prod, *ortho*-ether + *ortho* sulfone), 7.59 ( $H_F$ , d,  $J$  = 2.0 Hz, SM), 7.70-7.89 ( $H_D$  +  $H_F$ , m, SM + Prod, *ortho*-ether + *ortho* sulfone);  $\delta_C$  (75.5 MHz;  $CDCl_3$ ); 24.9, 25.3, 31.4, 42.8, 84.2, 116.9, 117.4, 118.2, 120.1, 120.2, 121.8, 129.7, 129.8, 129.9, 130.1, 130.5, 132.9, 134.7, 147.7, 153.2, 162.4;  $\delta_B$  (96 MHz;  $CDCl_3$ ); 23.3

#### 6.4.5 *Ortho*-ether Neopentyl Glycol Borate PSF (4.5)

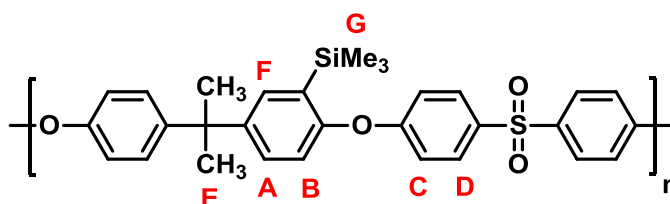


Following the general method of *ortho*-ether lithiation, brominated PSF **2.27** **DS** = **2.0** (1 g, 1.67 mmol) was lithiated with 2.5M *n*-BuLi (0.8 mL, 2 mmol) in anhydrous THF (25 mL) and quenched with excess 2-Isopropoxy-5,5-dimethyldioxaborinane **4.4** (2 mL) followed by precipitating into anhydrous hexane to give the title compound with a degree of substitution of 1.0.

$\delta_H$  (300 MHz;  $CDCl_3$ ); 0.71 ( $H_H$ , s, Prod), 0.73 ( $H_H$ , s, Prod), 0.85-1.00 ( $H_H$ , m, Prod, Minor), 1.69 ( $H_E$ , s, SM), 1.71 ( $H_E$ , s, Prod), 3.51 ( $H_G$ , s, Prod), 6.80-7.05 ( $H_B$  +  $H_C$ , m,

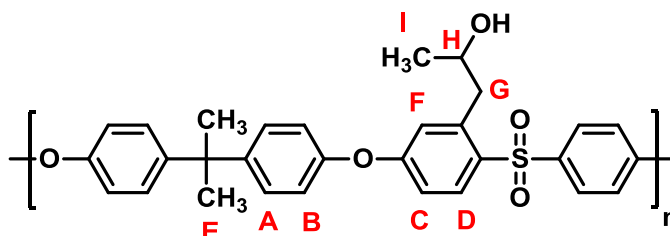
SM + Prod), 7.12-7.19 ( $H_A$ , m, SM), 7.19-7.29 ( $H_A$ , m, Prod), 7.51 ( $H_F$ , s, SM), 7.69 ( $H_F$ , s, Prod), 7.73-7.90 ( $H_D$ , m, SM + Prod);  $\delta_C$  (75.5 MHz;  $CDCl_3$ ); 21.6, 30.1, 31.5, 42.6, 72.3, 115.6, 116.6, 117.0, 117.1, 117.7, 119.8, 121.2, 121.5, 122.0, 127.7, 127.8, 128.5, 129.4, 129.8, 131.5, 132.3, 134.0. Aromatic quaternary carbons not observed;  $\delta_B$  (96 MHz;  $CDCl_3$ ); 21.0

#### 6.4.6 *Ortho*-ether Trimethylsilylated PSF (4.6)



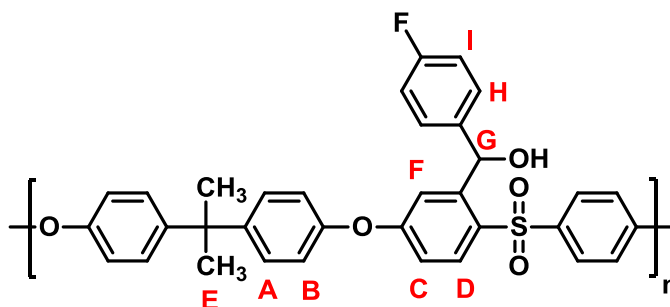
Following the general method of *ortho*-ether lithiation, brominated PSF **2.27**  $DS = 2.0$  (4.5 g, 7.5 mmol) was lithiated with 1.6M *n*-BuLi (10 mL, 16 mmol) in anhydrous THF (150 mL) and quenched with excess TMSCl (7.6 mL, 60mmol), the temperature lowered to  $-41^\circ C$  (dry ice/acetonitrile) for 30 minutes followed by precipitating into isopropanol to give the title compound with a degree of substitution of 1.5 as a 13:2 mixture of the *ortho*-ether and *ortho*-sulfone product.

$\delta_H$  (300 MHz;  $CDCl_3$ ); 0.14-0.18 ( $H_G$ , m, Prod, *ortho*-ether), 0.35-0.38 ( $H_G$ , m, Prod, *ortho*-sulfone), 1.68-1.73 ( $H_E$ , m, SM + Prod), 6.78 ( $H_B$ , d,  $J = 8.4$  Hz, Prod), 6.91-7.03 ( $H_C$ , m, SM + Prod), 7.19-7.28 ( $H_A$ , m, SM + Prod), 7.22 ( $H_A$ , dd,  $J = 8.4, 2.5$  Hz, Prod), 7.34 ( $H_F$ , d,  $J = 2.5$  Hz, Prod), 7.53-7.55 ( $H_F$ , br. s, SM), 7.71-7.77 ( $H_D$ , m, Prod, *ortho*-sulfone), 7.82-7.89 ( $H_D$ , m, SM + Prod, *ortho*-ether);  $\delta_C$  (75.5 MHz;  $CDCl_3$ ); 0.9, 1.2, 31.0, 42.6, 116.9, 117.5, 118.8, 119.8, 127.7, 128.4, 129.5, 129.7, 130.9, 133.8, 135.1, 146.4, 157.6, 162.1

6.4.7 *Ortho*-ether Isopropylated PSF (4.10)

Following the general method of *ortho*-sulfone lithiation, PSF **2.20** (1 g, 2.26 mmol) was lithiated with 2.5M *n*-BuLi (0.72 mL, 1.79 mmol) in anhydrous THF (25 mL).  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (0.22 mL, 1.79 mmol) was added followed by ( $\pm$ ) propylene oxide (0.032 mL, 0.45 mmol) and quenched with  $\text{NH}_4\text{Cl}$  before precipitating into EtOH to give the title compound with a degree of substitution of 0.10-0.15.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ); 1.24 ( $\text{H}_{\text{I}}$ , d,  $J = 6.2$  Hz, Prod), 1.69 ( $\text{H}_{\text{E}}$ , s, SM + Prod), 2.26-2.50 (OH, br. s, Prod), 2.87 ( $\text{H}_{\text{G}}$ , dd,  $J = 13.7, 8.2$  Hz, Prod), 2.97 ( $\text{H}_{\text{G}}$ , dd,  $J = 13.7, 4.2$  Hz, Prod), 3.88-4.03 ( $\text{H}_{\text{H}}$ , m, Prod), 6.94 ( $\text{H}_{\text{B}}$ , d,  $J = 8.7$  Hz, SM + Prod), 7.00 ( $\text{H}_{\text{C}} + \text{H}_{\text{F}}$ , d,  $J = 8.9$  Hz, SM + Prod), 7.24 ( $\text{H}_{\text{A}}$ , d,  $J = 8.7$  Hz, SM + Prod), 7.77 ( $\text{H}_{\text{D}}$ , d,  $J = 8.9$  Hz, Prod), 7.85 ( $\text{H}_{\text{D}}$ , d,  $J = 8.9$  Hz, SM), 8.05 ( $\text{H}_{\text{D}}$ , d,  $J = 8.9$  Hz, Prod)

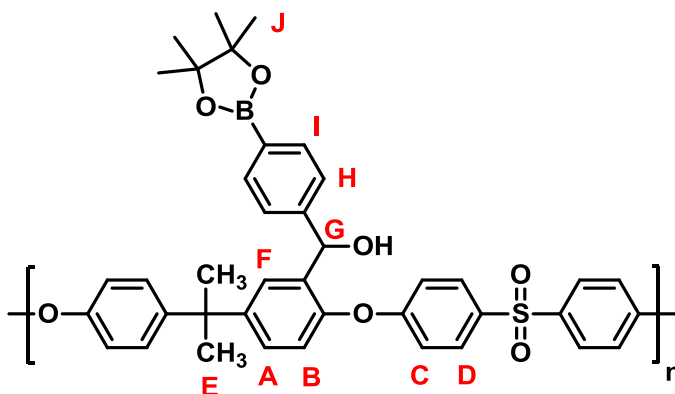
6.4.8 *Ortho*-ether 4-Fluorobenzyl Alcohol PSF (4.11)



Following the general method of *ortho*-sulfone lithiation, PSF **2.20** (1 g, 2.26 mmol) was lithiated with 2.5M *n*-BuLi (1.6 mL, 4 mmol) in anhydrous THF (25 mL) and quenched with excess 4-fluorobenzaldehyde (1.62 mL, 15 mmol) followed by NH<sub>4</sub>Cl before precipitating into EtOH to give the title compound with a degree of substitution of 1.10.

$\delta_H$  (300 MHz; CDCl<sub>3</sub>); 1.67 (H<sub>E</sub>, s, SM + Prod), 3.31 (OH, br.s, Prod), 6.47 (H<sub>G</sub>, s, Prod), 6.86-7.24 (H<sub>A</sub> + H<sub>B</sub> + H<sub>C</sub> + H<sub>F</sub> + H<sub>H</sub> + H<sub>I</sub>, m, SM + Prod), 7.71 (H<sub>D</sub>, d,  $J = 6.1$  Hz, Prod), 7.84 (H<sub>D</sub>, d,  $J = 8.9$  Hz, Prod), 8.06 (H<sub>D</sub>, d,  $J = 8.9$  Hz, Prod);  $\delta_C$  (75.5 MHz; CDCl<sub>3</sub>); 31.3, 42.8, 77.6, 115.3, 115.6, 116.2, 117.9, 118.1, 119.4, 120.2, 128.5, 128.6, 128.7, 128.8, 128.9, 129.8, 130.1, 132.4, 147.7, 152.7, 162.5;  $\delta_F$  (376 MHz; CDCl<sub>3</sub>); 114.6

#### 6.4.9 *Ortho*-sulfone 4-Pinacolboronic Ester Benzyl Alcohol PSF (4.15)

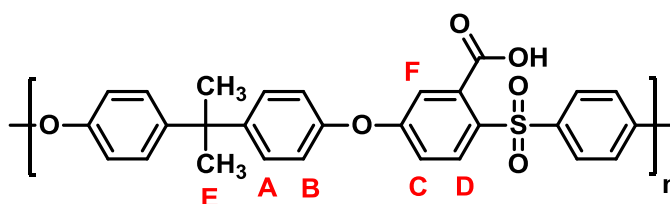


Following the general method of *ortho*-ether lithiation, brominated PSF **2.27** DS = **0.80** (1 g, 1.98 mmol) was lithiated with 2.5M *n*-BuLi (0.64 mL, 1.6 mmol) in anhydrous THF (25 mL) and quenched with excess 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde **4.13** (26 g, 1.12 mmol) followed by NH<sub>4</sub>Cl before precipitating into EtOH to give the title compound with a degree of substitution of 0.2.

$\delta_H$  (300 MHz; CDCl<sub>3</sub>); 1.37 (H<sub>I</sub>, s, Prod), 1.76 (H<sub>E</sub>, s, SM + Prod), 6.02 (H<sub>G</sub>, s, Prod), 6.80 (H<sub>B</sub>, d,  $J = 8.7$  Hz, Prod), 6.92 (H<sub>B</sub>, d,  $J = 8.7$  Hz, Prod), 6.99-7.04 (H<sub>B</sub> + H<sub>C</sub>, m, SM + Prod), 7.10 (H<sub>C</sub>, d,  $J = 8.7$  Hz, SM), 7.23 (H<sub>A</sub>, dd,  $J = 8.7, 2.3$  Hz, Prod), 7.31 (H<sub>A</sub> + H<sub>H</sub>,

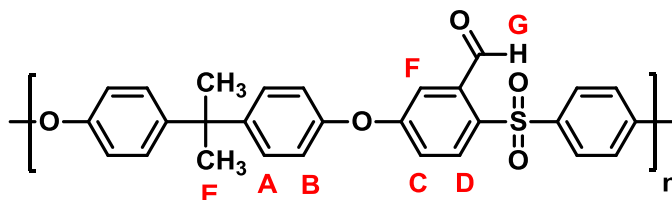
m, SM + Prod), 7.58 (H<sub>F</sub>, d,  $J$  = 2.1 Hz, SM), 7.64 (H<sub>F</sub>, d,  $J$  = 2.1 Hz, Prod), 7.73 (H<sub>I</sub>, d,  $J$  = 7.6 Hz, Prod), 7.83 (H<sub>D</sub>, d,  $J$  = 8.8 Hz, Prod), 7.91 (H<sub>D</sub>, d,  $J$  = 8.6 Hz, SM);  $\delta_C$  (75.5 MHz; CDCl<sub>3</sub>); 25.3, 31.4, 42.8, 117.4, 118.1, 120.2, 122.4, 126.2, 128.1, 128.8, 130.1, 132.6, 135.3, 135.8, 147.6, 153.2, 162.4

#### 6.4.10 Carboxylated PSF (4.18)



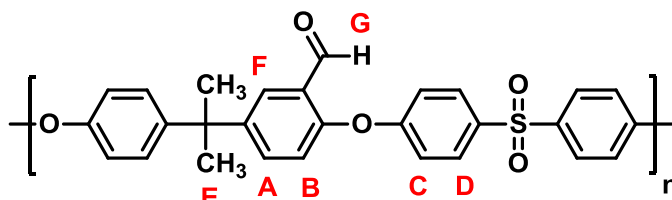
A stirred solution of PSF **2.20** (2.5 g, 5.65 mmol) in anhydrous THF (100 ml) was cooled to -41 °C (dry ice/acetonitrile) under a N<sub>2</sub> atmosphere. 2.5M *n*-BuLi (3.4 ml, 8.5 mmol) was added drop wise *via* a syringe pump at a rate of 30 mL/h to generate *ortho*-sulfone lithiated PSF in quantitative yield. After 30 minutes excess dry ice (2.5 g, 56.6 mmol) is added in one portion and the reaction, taking care, is vigorously shaken still submerged in the cooling bath. Once the viscosity lowers, the solution is allowed to warm to room temperature overnight. Upon quenching with dilute HCl the mixture is poured into a large quantity of stirred EtOH, filtered, redissolved and precipitated 2 more times before finally being filtered and washed with water and then dried in a vacuum oven at 40 °C over 2 days to give the title compound with a degree of substitution of 1.20.

$\delta_H$  (300 MHz; DMSO-*d*<sub>6</sub>); 1.63 (H<sub>E</sub>, s, SM + Prod), 6.94-7.14 (H<sub>B</sub> + H<sub>C</sub> + H<sub>F</sub>, m, SM + Prod), 7.20-7.35 (H<sub>A</sub>, m, SM + Prod), 7.83-7.94 (H<sub>D</sub>, m, SM + Prod), 7.98-8.09 (H<sub>D</sub>, m, Prod);  $\delta_C$  (75.5 MHz; DMSO-*d*<sub>6</sub>); 30.1, 42.4, 116.8, 116.9, 117.7, 118.5, 118.5, 120.0, 120.2, 128.8, 128.9, 130.7, 131.8, 132.9, 133.5, 135.4, 136.9, 137.2, 152.4, 152.7, 161.3, 161.7, 167.7, 167.9



$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ); 1.69 ( $\text{H}_{\text{E}}$ , s, SM + Prod), 6.79-7.16 ( $\text{H}_{\text{B}}$  +  $\text{H}_{\text{C}}$ , m, SM + Prod), 7.15-7.33 ( $\text{H}_{\text{A}}$  +  $\text{H}_{\text{C}}$ , m, SM + Prod), 7.49 ( $\text{H}_{\text{F}}$ , d,  $J = 2.2$  Hz, Prod, Mono), 7.52 ( $\text{H}_{\text{F}}$ , d,  $J = 2.5$  Hz, Prod, Di), 7.79 ( $\text{H}_{\text{D}}$ , d,  $J = 8.8$  Hz, Prod, Mono), 7.84 ( $\text{H}_{\text{D}}$ , d,  $J = 8.8$  Hz, SM), 7.95-8.15 ( $\text{H}_{\text{D}}$ , m, Prod, Mono + Di), 10.63 ( $\text{H}_{\text{G}}$ , s, Prod, Di), 10.78 ( $\text{H}_{\text{G}}$ , s, Prod, Mono);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ); 31.3, 43.0, 117.5, 118.2, 120.5, 121.7, 129.1, 130.0, 132.4. Aromatic quaternary carbons and aldehyde carbon not observed.

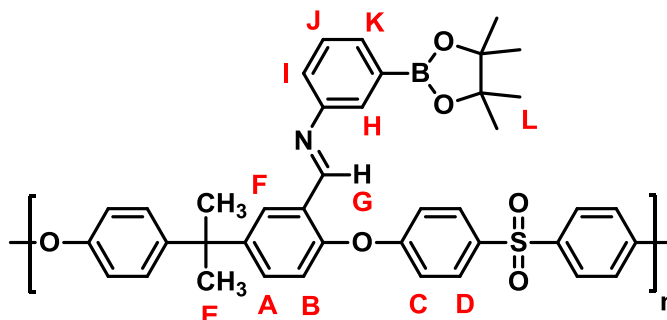
#### 6.4.12 *Ortho*-ether Formylated PSF (3.6)



Following the general method of *ortho*-sulfone lithiation, brominated PSF **2.27** **DS** = **2.0** (4.5 g, 7.5 mmol) was lithiated with 1.6M *n*-BuLi (10 mL, 15.75 mmol) in anhydrous THF (100 mL). It is subsequently quenched with a mixture of excess DMF (12 mL, 157.5 mmol) dissolved in THF (20 mL) cooled to -78 °C followed by HCl before precipitating into EtOH to give the title compound with a degree of substitution of 1.80.

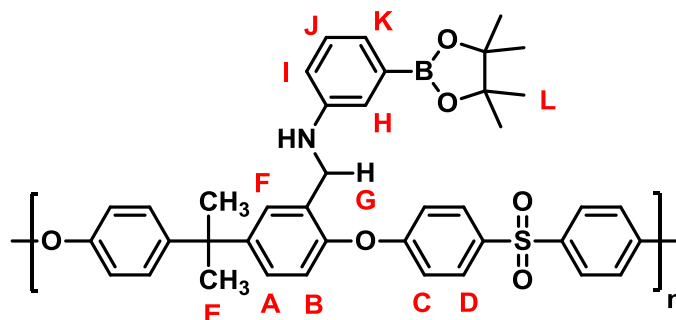
$\delta_H$  (300 MHz; CDCl<sub>3</sub>); 1.73 (H<sub>E</sub>, s, SM + Prod), 6.92 (H<sub>B</sub>, d,  $J$  = 8.8 Hz, Prod, Di) 7.01 (H<sub>B</sub>, d,  $J$  = 8.9 Hz, Prod, Mono), 7.10 (H<sub>C</sub>, d,  $J$  = 8.8 Hz, Prod, Di), 7.22 (H<sub>C</sub>, d, Mono), 7.41 (H<sub>A</sub>, dd,  $J$  = 8.7, 2.5 Hz, Prod), 7.85 (H<sub>F</sub>, d,  $J$  = 2.5 Hz, Prod), 7.92 (H<sub>D</sub>, d,  $J$  = 8.8 Hz, SM + Prod), 10.28 (H<sub>G</sub>, s, Prod);  $\delta_C$  (75.5 MHz; CDCl<sub>3</sub>); 30.6, 42.7, 118.5, 120.1, 120.4, 127.2, 128.4, 130.1, 134.8, 136.5, 146.9, 155.8, 161.2, 188.

#### 6.4.13 *Ortho*-ether Imine Boronic Pinacol Ester PSF (4.22)



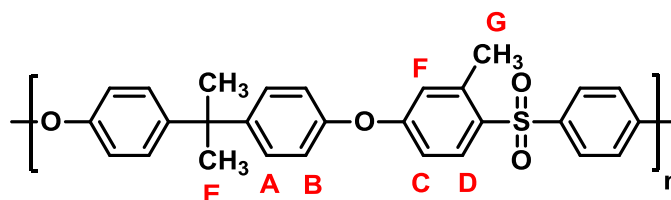
PSF **3.6** **DS** = **2.0** (0.65 g, 1.3 mmol) was dissolved in anhydrous THF (10 mL) with 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **4.21** (0.63 g, 2.9 mmol) and stirred for 12 hours. Following this NaBH(OAc)<sub>3</sub> (0.83 g, 3.9 mmol) was added to the mixture and stirred for a further 24 hours and then precipitated by pouring into EtOH. After filtration and washing the intermediate imine product was isolated at a degree of substitution of 0.90.

$\delta_H$  (300 MHz; CDCl<sub>3</sub>); 1.22-1.28 (H<sub>L</sub>, m, Prod), 1.60-1.78 (H<sub>E</sub>, m, SM + Prod), 6.7-7.3 (ArH, m, SM + Prod), 7.47 (H<sub>H</sub>, br. s, Prod), 7.57 (H<sub>I</sub>, d,  $J$  = 7.3 Hz, Prod), 7.75-7.87 (H<sub>D</sub>, m, SM + Prod), 8.19 (H<sub>F</sub>, s, Prod), 8.59 (H<sub>G</sub>, br. s, Prod), 10.2 (CHO, d,  $J$  = 2.6 Hz, SM)

6.4.14 *Ortho*-ether Amine Boronic Pinacol Ester PSF (4.23)

PSF **3.6** **DS** = **0.8** (5 g, 11 mmol) was dissolved in anhydrous THF (50 mL) with 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **4.21** (2.63 g, 12 mmol) and stirred for 12 hours. Following this  $\text{NaBH}_4$  (0.57 g, 15 mmol) was added to the mixture and stirred for a further 24 hours and then precipitated by pouring into EtOH. After filtration and washing the amine product was isolated at 1:1 ratio with the intermediate imine.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ); 0.92-1.36 ( $\text{H}_{\text{L}}$ , m, Prod), 1.63-1.82 ( $\text{H}_{\text{E}}$ , m, SM + Prod), 3.67-3.77 (m, reduced starting material), 4.24 ( $\text{NH}$ , br. s, Prod), 4.59 ( $\text{H}_{\text{G}}$ , br. s, Prod), 6.78-7.43 ( $\text{ArH}$ , m, SM + Prod), 7.54 ( $\text{H}_{\text{H}}$ , s, Prod), 7.63 ( $\text{H}_{\text{I}}$ , d,  $J = 7.2$  Hz, Prod), 7.76-7.89 ( $\text{H}_{\text{D}}$ , m, SM + Prod), 8.24 ( $\text{H}_{\text{F}}$ , s, Prod), 8.66 ( $\text{H}_{\text{G}}$ , s, SM), 10.29 ( $\text{CHO}$ , s, SM)

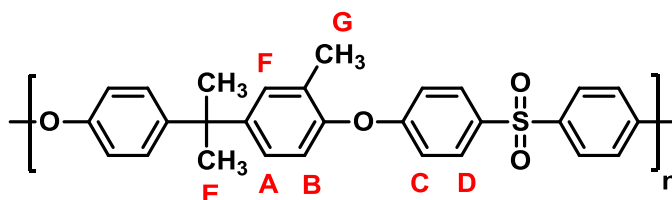
6.4.15 *Ortho*-sulfone Methylated PSF (4.24)

Following the general method of *ortho*-sulfone lithiation, PSF **2.20** (1 g, 2.26 mmol) was lithiated with 2.5M *n*-BuLi (1.9 mL, 4.75 mmol) in anhydrous THF (25 mL) and quenched

with excess MeI (0.6 mL, 9.5 mmol) followed by precipitating into MeOH to give the title compound with a degree of substitution of 1.60.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ); 1.70 ( $\text{H}_{\text{E}}$ , s, SM + Prod), 2.30 ( $\text{H}_{\text{G}}$ , s, Prod), 2.40 ( $\text{H}_{\text{G}}$ , s, Prod), 6.79-6.82 (m), 6.87 (dt,  $J = 8.8$ , 2.5 Hz), 6.92-6.98 ( $\text{H}_{\text{B}}$ , m, SM + Prod), 7.00 ( $\text{H}_{\text{C}}$ , d,  $J = 8.9$  Hz), 7.21-7.30 ( $\text{H}_{\text{A}}$ , m, SM + Prod), 7.75-7.81 ( $\text{H}_{\text{D}}$ , d,  $J = 8.8$ , Prod), 8.12 ( $\text{H}_{\text{D}}$ , d,  $J = 8.7$ , Prod)

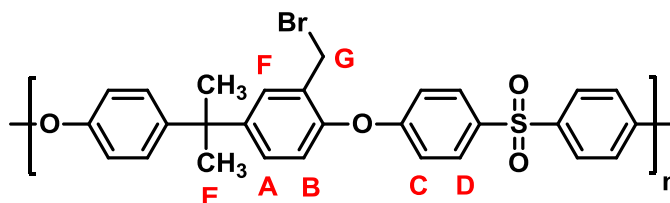
#### 6.4.16 *Ortho*-ether Methylated PSF (4.25)



Following the general method of *ortho*-ether lithiation, brominated PSF **2.27** **DS** = **2.0** (13.8 g, 23 mmol) was lithiated with 2.5M *n*-BuLi (19.32 mL, 48.3 mmol) in anhydrous THF (250 mL) and quenched with excess MeI (5.7 mL, 386 mmol) followed by precipitating into MeOH to give the title compound with a degree of substitution of 2.1.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ); 1.69 ( $\text{H}_{\text{E}}$ , s, Prod), 2.10 ( $\text{H}_{\text{G}}$ , s, Prod, *ortho*-ether), 2.39 ( $\text{H}_{\text{G}}$ , br. s, Prod, *ortho*-sulfone), 6.80 ( $\text{H}_{\text{B}}$ , d,  $J = 8.4$  Hz, Prod), 6.91 ( $\text{H}_{\text{C}}$ , d,  $J = 8.8$  Hz, Prod), 7.03-7.11 ( $\text{H}_{\text{A}}$ , br. d,  $J = 8.4$  Hz, Prod), 7.13 ( $\text{H}_{\text{F}}$ , br.s, Prod), 7.73-7.89 ( $\text{H}_{\text{D}}$ , m, Prod);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ); 16.4, 31.0, 42.3, 116.3, 116.5, 119.8, 120.4, 126.0, 128.4, 129.7, 130.1, 134.9, 147.7, 150.4, 162.1

#### 6.4.16 *Ortho*-ether Bromomethylated PSF (4.26)



To a solution of *ortho*-ether methylated PSF **4.25** DS = **1.67** (1 g, 2.15 mmol) dissolved in DCM (20 mL) was added NBS (0.63 g, 3.6 mol) and AIBN (0.035 g, 0.22 mmol) whereupon the mixture was refluxed for 24 hours. Following this the mixture was precipitated into MeOH, washed and filtered before drying in a vacuum oven at 40 °C to give the title compound of a degree of substitution of 1.20.

$\delta_{\text{H}}$  (300 MHz;  $\text{CDCl}_3$ ); 1.70 ( $\text{H}_{\text{E}}$ , m, SM + Prod), 4.44 ( $\text{H}_{\text{G}}$ , s, Prod), 6.82 ( $\text{H}_{\text{B}}$ , d,  $J = 8.5$  Hz, Prod), 6.86-7.01 ( $\text{H}_{\text{B}} + \text{H}_{\text{C}}$ , m, SM), 7.05 ( $\text{H}_{\text{C}}$ , d,  $J = 8.9$  Hz, Prod), 7.14 ( $\text{H}_{\text{A}}$ , dd,  $J = 8.5, 2.3$  Hz, Prod), 7.33 ( $\text{H}_{\text{F}}$ , d,  $J = 2.3$  Hz, Prod), 7.80-7.85 ( $\text{H}_{\text{D}}$ , m, SM), 7.88 ( $\text{H}_{\text{D}}$ , d,  $J = 8.8$  Hz, Prod);  $\delta_{\text{C}}$  (75.5 MHz;  $\text{CDCl}_3$ ); 16.36, 27.7, 30.8, 42.5, 116.6, 117.7, 118.0, 119.8, 120.0, 120.1, 126.0, 128.4, 129.0, 129.4, 129.8, 130.1, 135.9, 147.3, 151.3, 161.4

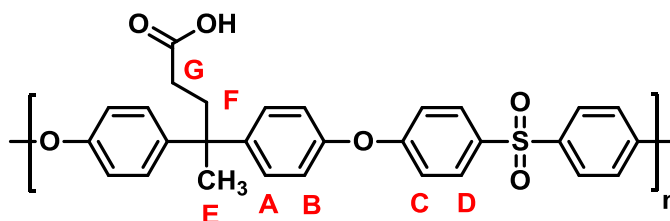
### 6.50 Polymerisation

#### 6.5.1 General Method of Polymerisation

To a solution of bisphenol dissolved in anhydrous DMSO or NMP with anhydrous toluene under an atmosphere of  $\text{N}_2$  was added  $\text{K}_2\text{CO}_3$ . A Dean Stark trap was attached and the mixture azeotropically refluxed to remove water. Following this 4,4'-dichlorodiphenyl sulfone **2.35** or 4,4'-difluorodiphenyl sulfone **5.4** was added and the reaction refluxed further. After cooling down the mixture separates and the solvent is decanted to leave a viscous mixture of  $\text{K}_2\text{CO}_3$  and polymer, to which is added a solution of 3:1 THF and concentrated HCl. Once the mixture solubilises it is poured into a large stirred amount of water to precipitate over 30 hours, subsequently being filtered, washed with water,

redissolved in THF and precipitated into EtOH. The final product is filtered and dried in a vacuum oven for 3 days at 40 °C.

### 6.5.2 Pentanoic Acid PSF (2.37-1) DS = 1.0



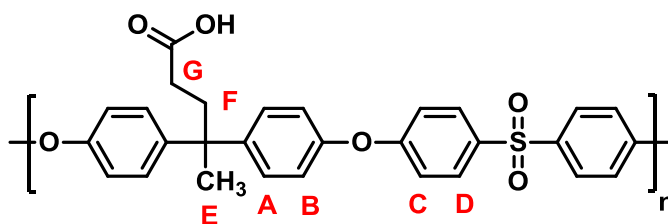
Following the general method of polymerisation, 4,4-bis(4'-hydroxyphenyl)pentanoic acid **2.36** (7.16 g, 25 mmol) in DMSO (60 mL) and toluene (30 mL) was stirred at reflux with  $K_2CO_3$  (7 g, 55 mmol) for 2 hours. Afterwards 4,4'-dichlorodiphenyl sulfone **2.35** (7.18 g, 25 mmol) was added and the reaction further refluxed for 12 hours. Once cooled and the top layer of solvent decanted, THF (150 mL) and conc. HCl (50 mL) were added followed by precipitation into 2 L of water, filtered, redissolved and then precipitating into 1.2 L of EtOH, generating the title compound after filtering and drying.

$\delta_H$  (300 MHz; DMSO- $d_6$ ); 1.57 ( $H_E$ , s.), 2.00 ( $H_F$ , br. s) 2.34 ( $H_G$ , br. s) 7.01 ( $H_B$ , d,  $J = 8.1$  Hz), 7.06 ( $H_C$ , d,  $J = 8.5$  Hz), 7.23 ( $H_A$ , d,  $J = 8.1$  Hz), 7.89 ( $H_D$ , d,  $J = 8.5$  Hz), 12.12 (COOH, br. s);  $\delta_C$  (75.5 MHz; DMSO- $d_6$ ); 27.3, 30.2, 36.3, 45.1, 118.2, 120.1, 129.2, 130.2, 135.5, 145.6, 152.8, 161.7, 174.8

GPC;  $M_n = 1900$  Da,  $M_w = 2600$  Da, PD = 1.36



## 6.5.3 Pentanoic Acid PSF (5.1) DS = 0.5

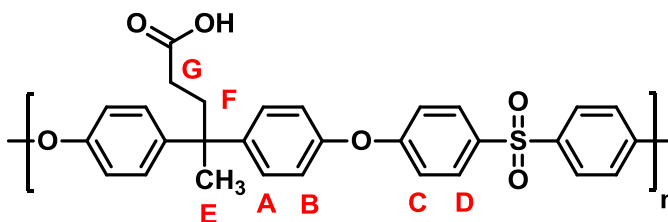


Following the general method of polymerisation, 4,4-bis(4'-hydroxyphenyl)pentanoic acid **2.36** (3.58 g, 12.5 mmol) and bisphenol A **2.34** (2.85 g, 12.5 mmol) in DMSO (60 mL) and toluene (30 mL) was stirred at reflux with  $K_2CO_3$  (7 g, 55 mmol) for 2 hours. Afterwards 4,4'-dichlorodiphenyl sulfone **2.35** (7.18 g, 25 mmol) was added and the reaction further refluxed for 12 hours. Once cooled and the top layer of solvent decanted, THF (150 mL) and conc. HCl (50 mL) were added followed by precipitation into 2 L of water, filtered, redissolved and then precipitating into 1.2 L of EtOH, generating the title compound after filtering and drying.

$\delta_H$  (300 MHz; DMSO); 1.5-1.65 ( $H_E$ , m), 2.00 ( $H_F$ , br. s), 2.33 ( $H_G$ , br. s), 6.88-7.12 ( $H_B + H_C$ , m), 7.23 ( $H_C$ , br. s), 7.86 ( $H_D$ , br. s), 12.07 (COOH, br. s);  $\delta_C$  (75.5 MHz; DMSO- $d_6$ ); 27.3, 30.2, 30.8, 118.1, 120.1, 128.7, 130.1, 135.5, 147.1, 152.8, 161.7, 174.8

GPC;  $M_n = 2400$  Da,  $M_w = 2700$  Da, PD = 1.135

## 6.5.4 Pentanoic Acid PSF (2.37-2) DS = 1.0

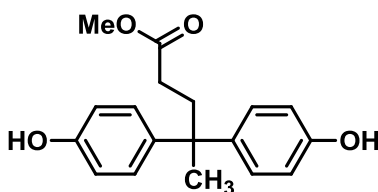


Following the general method of polymerisation, 4,4-bis(4'-hydroxyphenyl)pentanoic acid **2.36** (7.16 g, 25 mmol) in DMSO (60 mL) and toluene (30 mL) was stirred at reflux with  $K_2CO_3$  (11 g, 87 mmol) for 2 hours. Afterwards 4,4'-dichlorodiphenyl sulfone **2.35** (7.18 g, 25 mmol) was added and the reaction further refluxed for 12 hours. Once cooled and the top layer of solvent decanted, THF (150 mL) and conc. HCl (50 mL) were added followed by precipitation into 2 L of water, filtered, redissolved and then precipitating into 1.2 L of EtOH, generating the title compound after filtering and drying.

The NMR data is identical to that described previously.

GPC;  $M_n$  6700 Da,  $M_w$  = 5700 Da, PD = 1.21

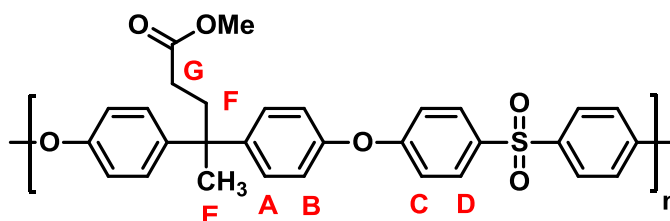
### 6.5.5 Methyl 4,4-bis(4-hydroxyphenyl)pentanoate (5.2)



To a solution of 4,4-bis(4'-hydroxyphenyl)pentanoic acid **2.36** (10 g, 35 mmol) in MeOH was added conc.  $H_2SO_4$  (1 mL) and the reaction stirred for 3 hours at room temperature. Following this the mixture was concentrated *in vacuo*, dissolved in  $Et_2O$  and washed with  $NaHCO_3$  and brine, and dried with  $NaSO_4$ . The organic layer was concentrated *in vacuo* and recrystallised from  $Et_2O$ /hexane to give the title compound in 95% yield (9.98 g, 33.3 mmol).

$\delta_H$  (300 MHz;  $CDCl_3$ ); 1.52 (3H, s,  $CH_3$ ), 2.08-2.17 (2H, m,  $CH_2$ ), 2.43-2.42 (2H, m,  $CH_2$ ), 3.62 (3H, s,  $OCH_3$ ), 6.2 (2H, br. s, OH), 6.71 (4H, d,  $J$  = 8.8 Hz,  $CH_2$ ), 6.99 (4H, d,  $J$  = 8.8 Hz,  $CH_2$ );  $\delta_C$  (75.5 MHz;  $DMSO-d_6$ ); 30.2, 36.6, 44.5, 51.8, 114.9, 128.5, 141.0, 153.6, 175.0

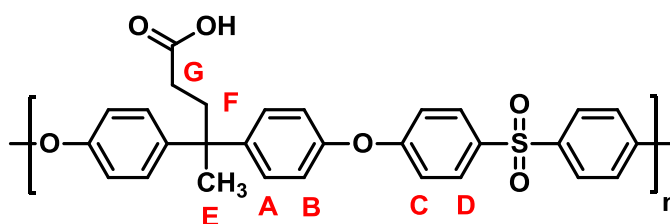
### 6.5.6 Methyl Pentanoate PSF (5.3) DS = 1.0



Following the general method of polymerisation, methyl 4,4-bis(4-hydroxyphenyl)pentanoate **5.2** (7.5 g, 25 mmol) in DMSO (60 mL) and toluene (30 mL) was stirred at reflux with K<sub>2</sub>CO<sub>3</sub> (7 g, 55 mmol) for 2 hours. Afterwards 4,4'-dichlorodiphenyl sulfone **2.35** (7.18 g, 25 mmol) was added and the reaction further refluxed for 12 hours. Once cooled and the top layer of solvent decanted, THF (150 mL) and conc. HCl (50 mL) were added followed by precipitation into 2 L of water, filtered, redissolved and then precipitating into 1.2 L of EtOH, generating the title compound after filtering and drying.

GPC; M<sub>n</sub> = 3550 Da, M<sub>w</sub> = 5250 Da, PD = 1.49

### 6.5.7 Pentanoic Acid PSF (2.37-3) DS = 1.0



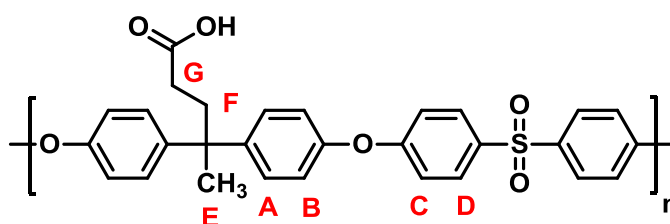
Following the general method of polymerisation, 4,4-bis(4'-hydroxyphenyl)pentanoic acid **2.36** (7.16 g, 25 mmol) in DMSO (60 mL) and toluene (30 mL) was stirred at reflux with K<sub>2</sub>CO<sub>3</sub> (11 g, 87 mmol) for 6 hours. Afterwards 4,4'-dichlorodiphenyl sulfone **2.35** (7.18 g, 25 mmol) was added and the reaction further refluxed for 24 hours. Once cooled and the top layer of solvent decanted, THF (150 mL) and conc. HCl (50 mL) were added followed

by precipitation into 2 L of water, filtered, redissolved and then precipitating into 1.2 L of EtOH, generating the title compound after filtering and drying.

The NMR data is identical to that described previously.

GPC;  $M_n$  6200 Da,  $M_w$  = 9450 Da, PD = 1.52

#### 6.5.8 Pentanoic Acid PSF (2.37-4)-(2.37-7) DS = 1.0



Following the general method of polymerisation, 4,4-bis(4'-hydroxyphenyl)pentanoic acid **2.36** (7.16 g, 25 mmol) in DMSO (60 mL) and toluene (30 mL) was stirred at reflux with  $K_2CO_3$  (11 g, 87 mmol) for 2 hours. Afterwards 4,4'-difluorodiphenyl sulfone **5.4** (6.36 g, 25 mmol) was added and the reaction further refluxed for 10 hours. Once cooled and the top layer of solvent decanted, THF (150 mL) and conc. HCl (50 mL) were added followed by precipitation into 2 L of water, filtered, redissolved and then precipitating into 1.2 L of EtOH, generating the title compound after filtering and drying.

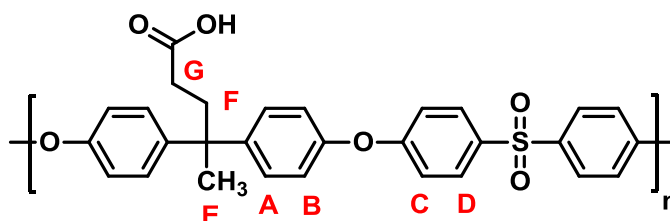
The NMR data is identical to that described previously.

**PSF (2.37-4)**; GPC;  $M_n$  = 6500 Da,  $M_w$  = 11000 Da, PD = 1.69

**PSF (2.37-5)**; GPC;  $M_n$  = 12000 Da,  $M_w$  = 18600 Da, PD = 1.55

**PSF (2.37-6)**; GPC;  $M_n$  = 18450 Da,  $M_w$  = 28700 Da, PD = 1.56

**PSF (2.37-7)**; GPC;  $M_n$  = 13050 Da,  $M_w$  = 13050 Da, PD = 1.61

**6.5.9 Pentanoic Acid PSF (2.37-8)-(2.37-10) DS = 1.0**

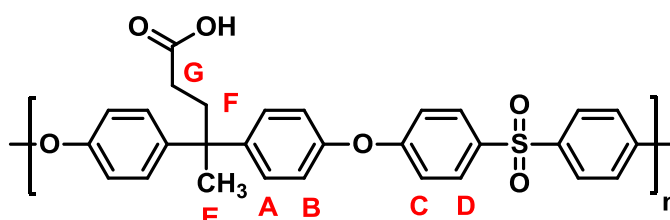
Following the general method of polymerisation, 4,4-bis(4'-hydroxyphenyl)pentanoic acid **2.36** (7.16 g, 25 mmol) in NMP (60 mL) and toluene (30 mL) was stirred at reflux with  $K_2CO_3$  (11 g, 87 mmol) for 6 hours. Afterwards 4,4'-difluorodiphenyl sulfone **5.4** (6.36 g, 25 mmol) was added and the reaction further refluxed for 6 hours. Once cooled and the top layer of solvent decanted, THF (150 mL) and conc. HCl (50 mL) were added followed by precipitation into 2 L of water, filtered, redissolved and then precipitating into 1.2 L of EtOH, generating the title compound after filtering and drying.

The NMR data is identical to that described previously.

**PSF (2.37-8)**; GPC;  $M_n = 37100$  Da,  $M_w = 64200$  Da, PD = 1.73

**PSF (2.37-9)**; GPC;  $M_n = 23600$  Da,  $M_w = 41400$  Da, PD = 1.76

**PSF (2.37-10)**; GPC;  $M_n = 23800$  Da,  $M_w = 51300$  Da, PD = 2.15

**6.5.10 Pentanoic Acid PSF (2.37-11)-(2.37-14) DS = 1.0**

Following the general method of polymerisation, 4,4-bis(4'-hydroxyphenyl)pentanoic acid **2.36** (7.16 g, 25 mmol) in NMP (60 mL) and toluene (30 mL) was stirred at reflux with  $K_2CO_3$  (11 g, 87 mmol) for 6 hours. Afterwards, the toluene was removed and 4,4'-difluorodiphenyl sulfone **5.4** (6.36 g, 25 mmol) was added with the reaction further refluxed for 6 hours. Once cooled and the top layer of solvent decanted, THF (150 mL) and conc. HCl (50 mL) were added followed by precipitation into 2 L of water, filtered, redissolved and then precipitating into 1.2 L of EtOH, generating the title compound after filtering and drying.

The NMR data is identical to that described previously.

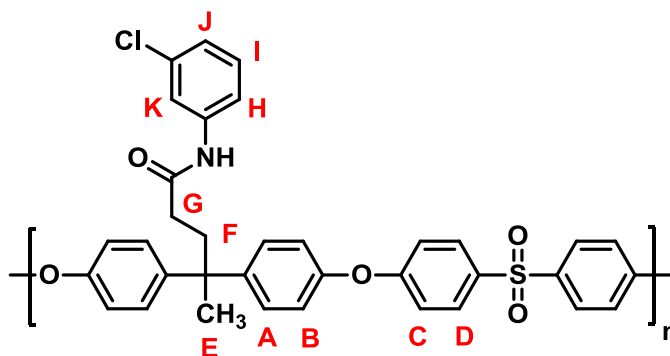
**PSF (2.37-11)**; GPC;  $M_n = 46350$  Da,  $M_w = 98700$  Da, PD = 2.13

**PSF (2.37-12)**; GPC;  $M_n = 37850$  Da,  $M_w = 255300$  Da, PD = 6.75

**PSF (2.37-13)**; GPC;  $M_n = 52700$  Da,  $M_w = 142150$  Da, PD = 2.70

**PSF (2.37-14)**; GPC;  $M_n = 11050$  Da,  $M_w = 155500$  Da, PD = 1.41

#### 6.5.11 *N*-(3-chlorophenyl)pentanamide PSF (**5.6**)

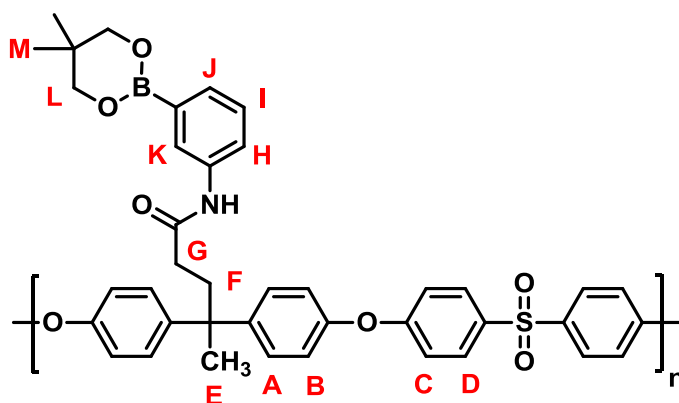


To a solution of PSF **5.1** (1.923 g, 2 mmol) in anhydrous THF (15 mL) was added oxalyl chloride (0.5 mL, 6 mmol) and stirred for 10 hours at room temperature. Following this the solvent and excess oxalyl chloride were removed *in vacuo*, the residue redissolved into anhydrous THF (15 mL) and excess 3-chloroaniline (2.12 mL, 20 mmol) added and the reaction stirred at room temperature for a further 24 hours. The polymer was obtained after

precipitation into 300 mL of EtOH, dissolution in THF and precipitation in Et<sub>2</sub>O and dried in a vacuum oven at 40 °C for 3 days to give a polymer with a degree of substitution of 0.65.

$\delta_H$  (300 MHz; DMSO-*d*<sub>6</sub>); 1.59 (H<sub>E</sub>, s, SM + Prod), 2.00-2.20 (H<sub>F</sub>, m, SM + Prod), 2.31-2.47 (H<sub>G</sub>, m, SM + Prod), 7.03 (H<sub>B</sub> + H<sub>C</sub> + H<sub>J</sub>, br. s, SM + Prod), 7.24 (H<sub>A</sub> + H<sub>I</sub>, br. s, SM + Prod), 7.38 (H<sub>H</sub>, d, *J* = 8.2 Hz, Prod), 7.77 (H<sub>K</sub>, s, Prod), 7.86 (H<sub>D</sub>, br. s, SM + Prod), 10.0 (NH, s, Prod);  $\delta_C$  (75.5 MHz; DMSO-*d*<sub>6</sub>); 27.6, 30.5, 30.8, 118.1, 120.1, 123.0, 128.7, 130.1, 133.3, 135.5, 141.0, 145.6, 147.1, 152.8, 161.7, 171.66.

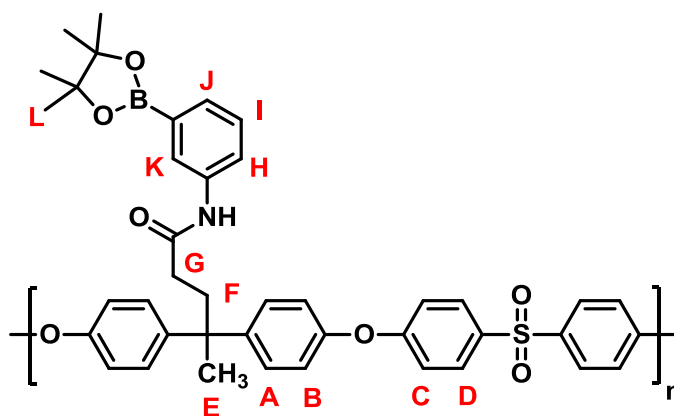
### 6.5.12 3-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)pentamide PSF (5.8)



To a solution of PSF **2.37-1** (1.38 g, 2.75 mmol) in anhydrous THF (15 mL) was added oxalyl chloride (0.69 mL, 8.25 mmol) and stirred for 10 hours at room temperature. Following this the solvent and excess oxalyl chloride were removed *in vacuo*, the residue redissolved into anhydrous THF (15 mL) and excess 3-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)aniline **5.7** (1.2 g, 5.5 mmol) added to the reaction with NEt<sub>3</sub> (0.29 mL, 2.1 mmol) and the reaction stirred at room temperature for a further 24 hours. The polymer was obtained after precipitation into 300 mL of EtOH, dissolution in THF and precipitation in Et<sub>2</sub>O and dried in a vacuum oven at 40 °C for 3 days to give a polymer with a degree of substitution of 0.78, with a 58:20 ratio of boronate ester to free boronic acid.

$\delta_H$  (300 MHz; DMSO- $d_6$ ); 0.86-0.95 ( $H_M$ , m, Prod), 1.50-1.72 ( $H_E$ , m, SM + Prod), 1.92-2.21 ( $H_F$ , m, SM + Prod), 2.24-2.50 ( $H_G$ , m, SM + Prod), 6.96-7.12 ( $H_B + H_C$ , m, SM + Prod), 7.17-7.34 ( $H_A + H_J + H_I$ , m, SM + Prod, Protected + Deprotected), 7.44 ( $H_J$ , d,  $J = 7.2$  Hz, Prod, Deprotected), 7.65 ( $H_H$ , d,  $J = 8.4$  Hz, Prod, Protected + Deprotected), 7.79 ( $H_K$ , br. s, Prod, Deprotected), 7.86 ( $H_D + H_K$ , br. s, SM + Prod, Protected), 7.95 (BOH, s, Product, Deprotected), 9.75 (NH, s, Product, Protected + Deprotected);  $\delta_C$  (75.5 MHz; DMSO- $d_6$ ); 21.6, 27.6, 31.8, 71.7, 118.2, 120.1, 121.7, 124.7, 128.2, 129.3, 130.2, 135.5, 139.0, 145.7, 152.8, 161.7

### 6.5.13 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentamide PSF (5.10)

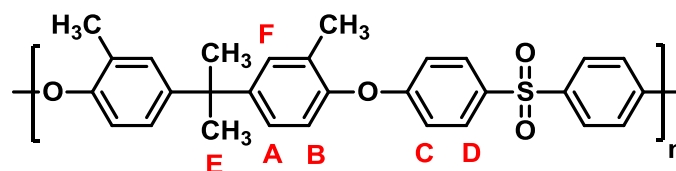


To a solution of PSF **2.37-11** (7.6 g, 15.2 mmol) in anhydrous THF (60 mL) was added oxalyl chloride (3.9 mL, 45.6 mmol) and stirred for 10 hours at room temperature. Following this the solvent and excess oxalyl chloride were removed *in vacuo*, the residue redissolved into anhydrous THF (60 mL) and excess 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline **4.21** (6.7 g, 30.4 mmol) added to the reaction with pyridine (6.05 mL, 75 mmol) and stirred at room temperature for a further 24 hours. The polymer was obtained after precipitation into 300 mL of EtOH, dissolution in THF and precipitation in Et<sub>2</sub>O and dried in a vacuum oven at 40 °C for 3 days to give a polymer with a degree of substitution of 0.60.



$\delta_{\text{H}}$  (300 MHz; DMSO- $d_6$ ); 1.20-1.34 ( $H_{\text{L}}$ , m, Prod), 1.52-1.66 ( $H_{\text{E}}$ , m, SM + Prod), 1.95-2.19 ( $H_{\text{F}}$ , m, SM + Prod), 2.23-2.42 ( $H_{\text{G}}$ , m, Prod), 6.93-7.91 ( $H_{\text{B}}$  +  $H_{\text{C}}$ , m, SM + Prod), 7.16-7.30 ( $H_{\text{A}}$ , m, SM + Prod), 7.32-7.49 ( $H_{\text{J}}$  +  $H_{\text{I}}$ , m, Prod), 7.69 ( $H_{\text{H}}$ , br. d,  $J = 8.2$  Hz, Prod), 7.83-7.94 ( $H_{\text{D}}$  +  $H_{\text{K}}$ , m, SM + Prod);  $\delta_{\text{C}}$  (75.5 MHz; DMSO- $d_6$ ); 25.0, 30.2, 45.1, 84.0, 118.1, 120.1, 123.9, 126.8, 129.2, 130.2, 135.5, 139.2, 145.5, 152.8, 159.0, 161.7, 174.7

#### 6.5.14 Dimethyl PSF (5.12)

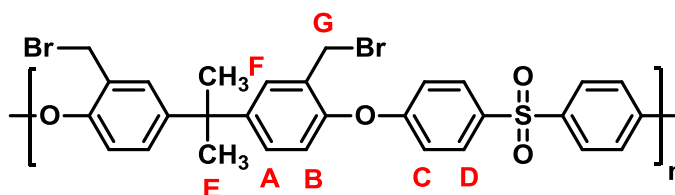


Following the general method of polymerisation, 2,2-bis(4-hydroxy-3-methylphenyl)propane **5.11** (3.2 g, 12.5 mmol) in NMP (40 mL) and toluene (60 mL) was stirred at reflux with  $\text{K}_2\text{CO}_3$  (3.5 g, 25 mmol) for 2 hours. Afterwards, the toluene was removed and 4,4'-difluorodiphenyl sulfone **5.4** (3.18 g, 12.5 mmol) was added with the reaction further refluxed for 4 hours. Once cooled and the top layer of solvent decanted, THF (100 mL) and conc. HCl (30 mL) were added followed by precipitation into 2 L of water, filtered, redissolved and then precipitating into 1.2 L of EtOH, generating the title compound after filtering and drying.

The NMR data is identical to that described previously.

GPC;  $M_n = 8100$  Da,  $13250$  Da, PD = 1.63

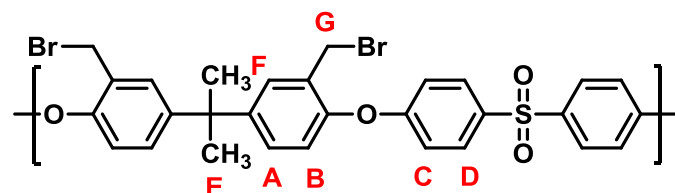
## 6.5.15 Bromomethyl PSF (5.13)



A solution of dimethyl PSF **5.12** (1.8 g, 3.83 mmol) in tetrachloroethane (24 mL) was heated to reflux under irradiation from a UV Lamp (0.2 Å Long Wave). Bromine (0.43 mL, 9 mmol) was added dropwise and the solution was refluxed for 1 hour after the addition. Upon completion the mixture was poured into MeOH, filtered, washed with MeOH and dried in a vacuum oven for 2 days to give the title compound with a degree of substitution of 0.99.

The NMR data is identical to that described previously.

## 6.5.15 Bromomethyl PSF (5.13)



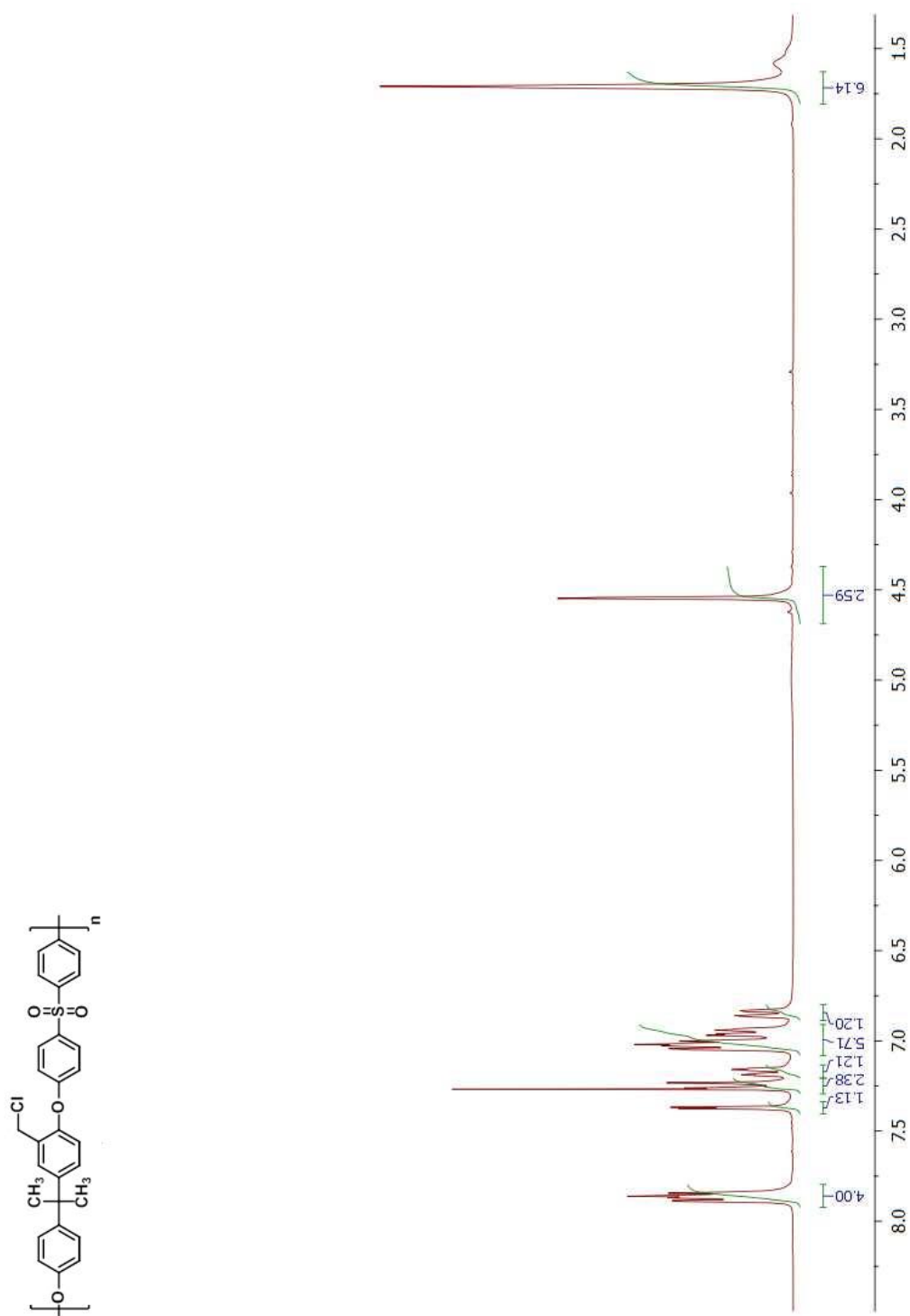
To a solution of dimethyl PSF **5.12** PSF (1 g, 2.22 mmol) dissolved in DCM (20 mL) was added NBS (0.63 g, 3.6mol) and AIBN (0.035g, 0.22 mmol) whereupon the mixture was refluxed for 24 hours. Following this the mixture was precipitated into MeOH, washed and filtered before drying in a vacuum oven at 40 °C to give the title compound of a degree of substitution of 1.44.

The NMR data is identical to that described previously.

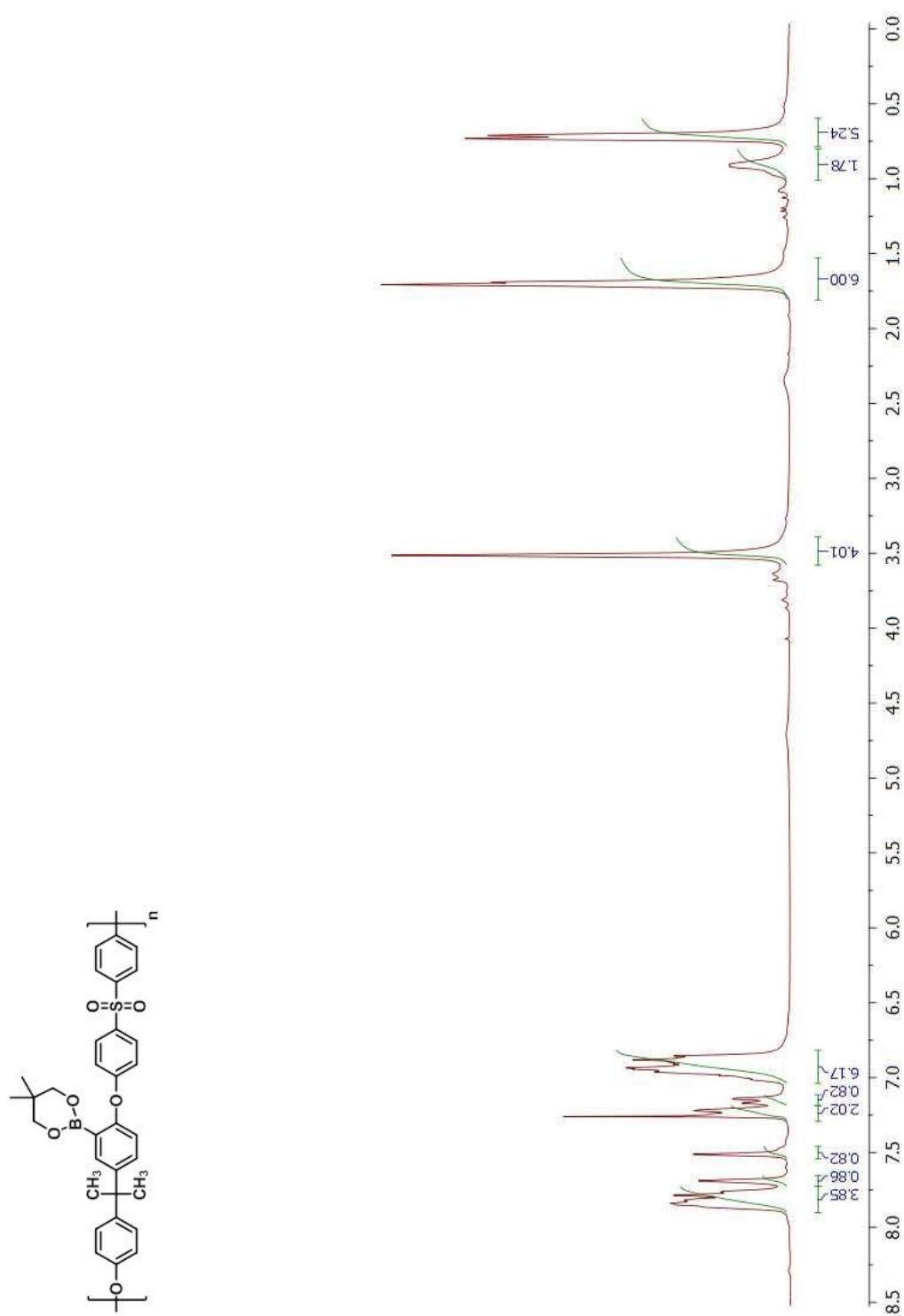
## 6.6 References

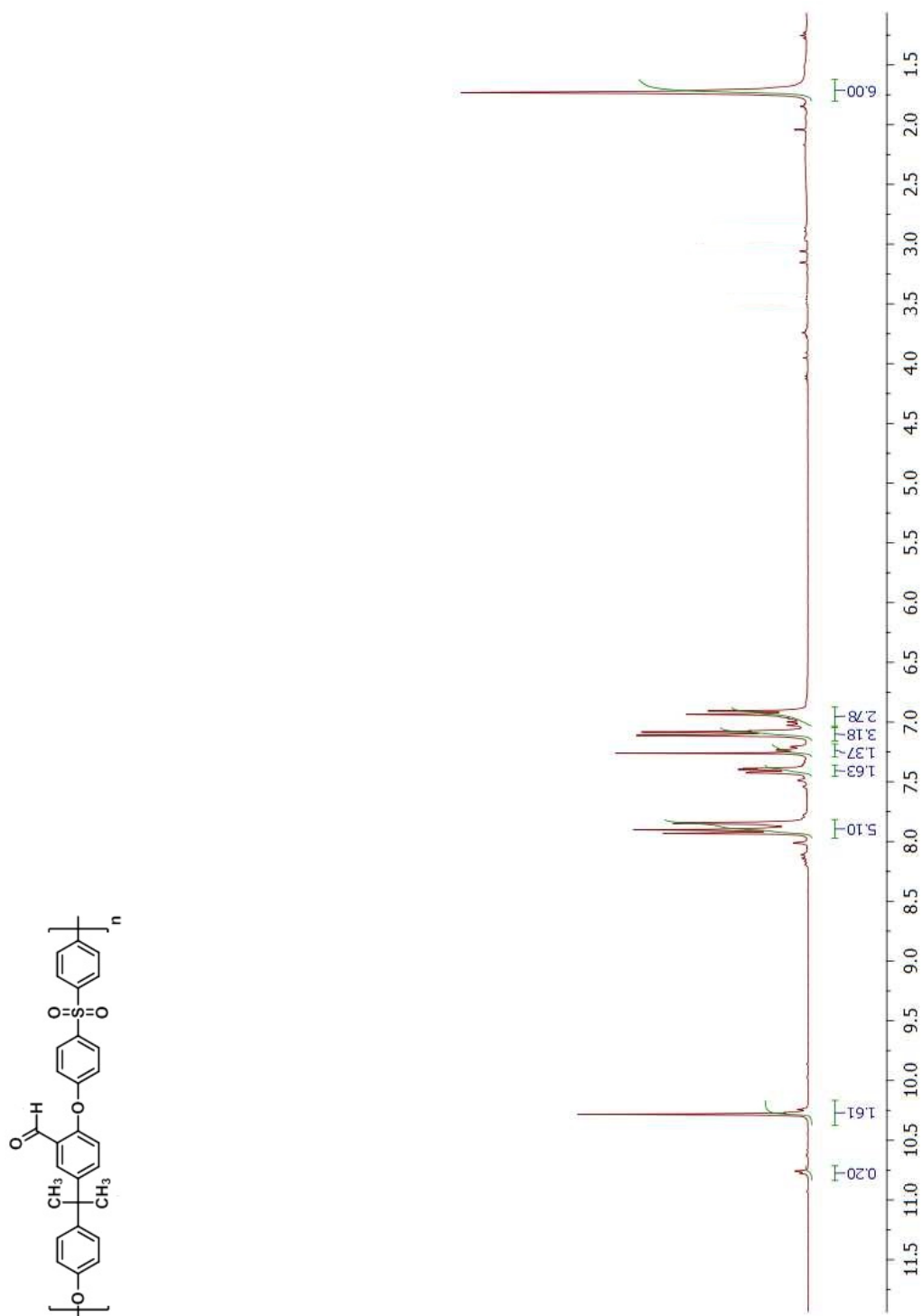
- (1) Noguchi, H.; Hojo, K.; Suginome, M. *J. Am. Chem. Soc.* **2007**, *129*, 758.
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- (4) Chow, W. K.; So, C. M.; Lau, C. P.; Kwong, F. Y. *Chem.--Eur. J.* **2011**, *17*, 6913.
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- (6) Andersen, M. W.; Hildebrandt, B.; Koster, G.; Hoffmann, R. W. *Chem. Ber.* **1989**, *122*, 1777.
- (7) Guiver, M. D.; Kutow, O.; Apsimon, J. W. *Polymer* **1989**, *30*, 1137.

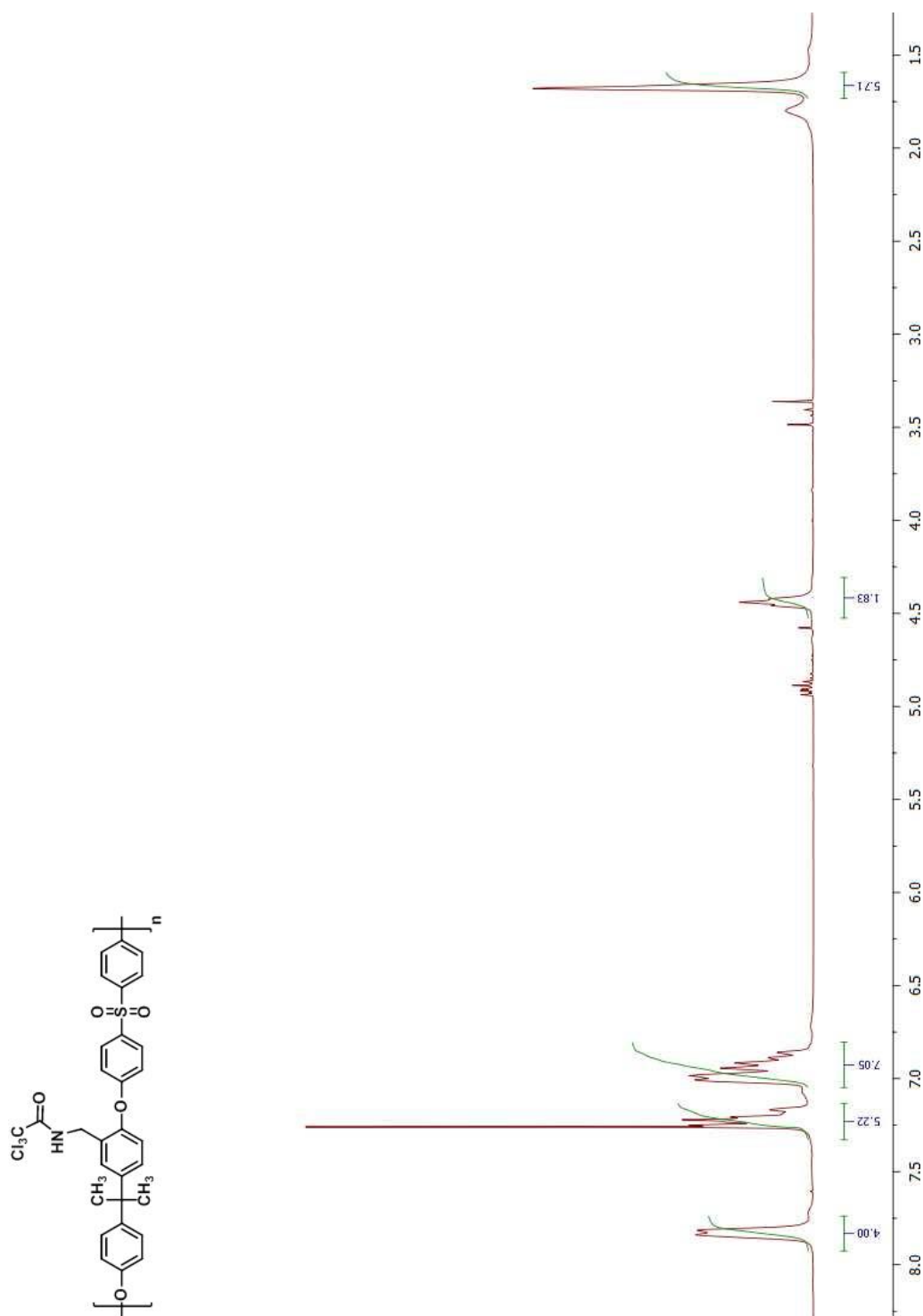
## **Appendix: Selected NMR Spectra**

**Chloromethylated PSF (3.1) –  $^1\text{H}$  NMR Spectrum (300 MHz,  $\text{CDCl}_3$ )**

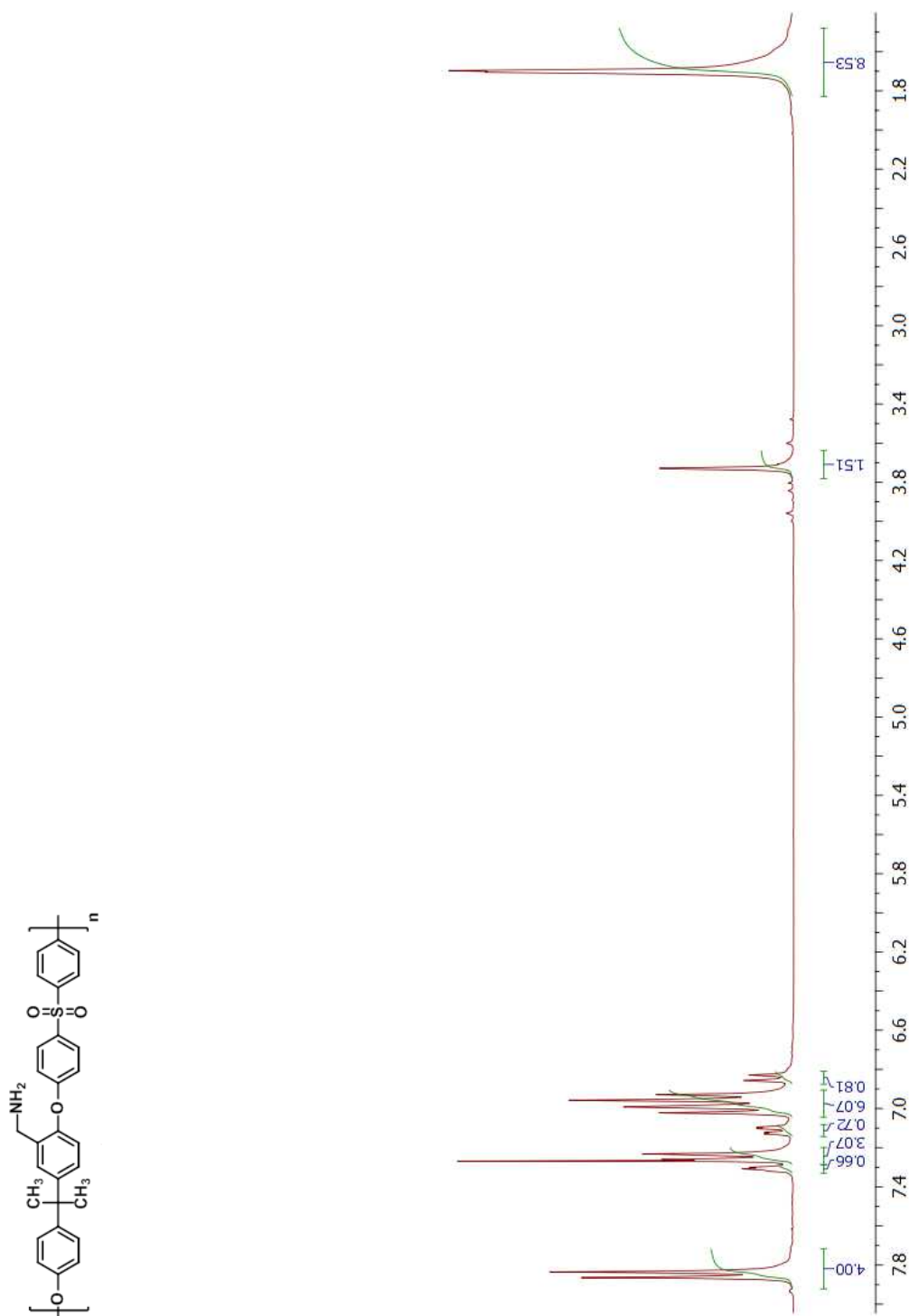
***Ortho*-ether Neopentyl Glycol Borate PSF (4.5) -  $^1\text{H}$  NMR Spectrum (300 MHz,  $\text{CDCl}_3$ )**

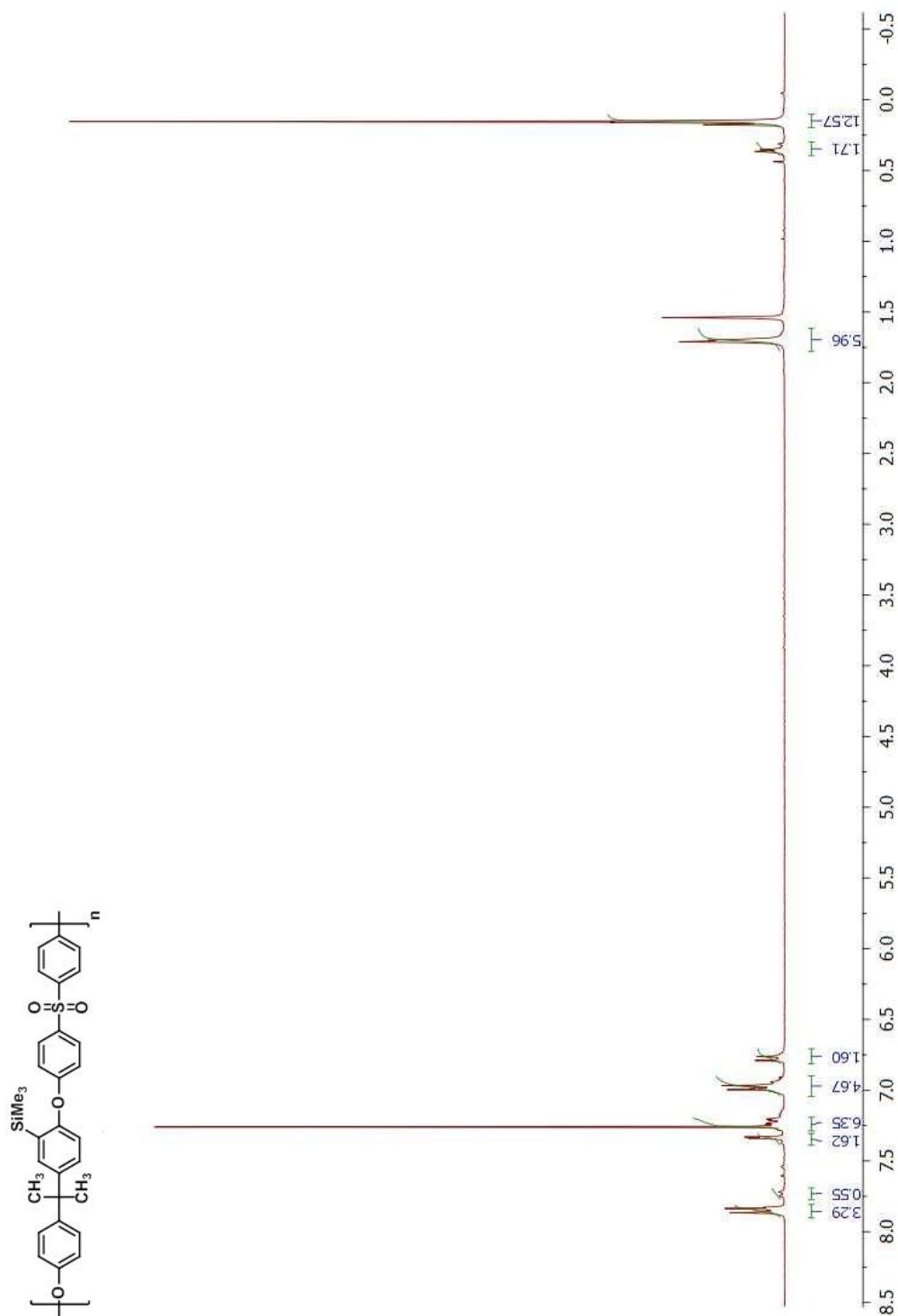


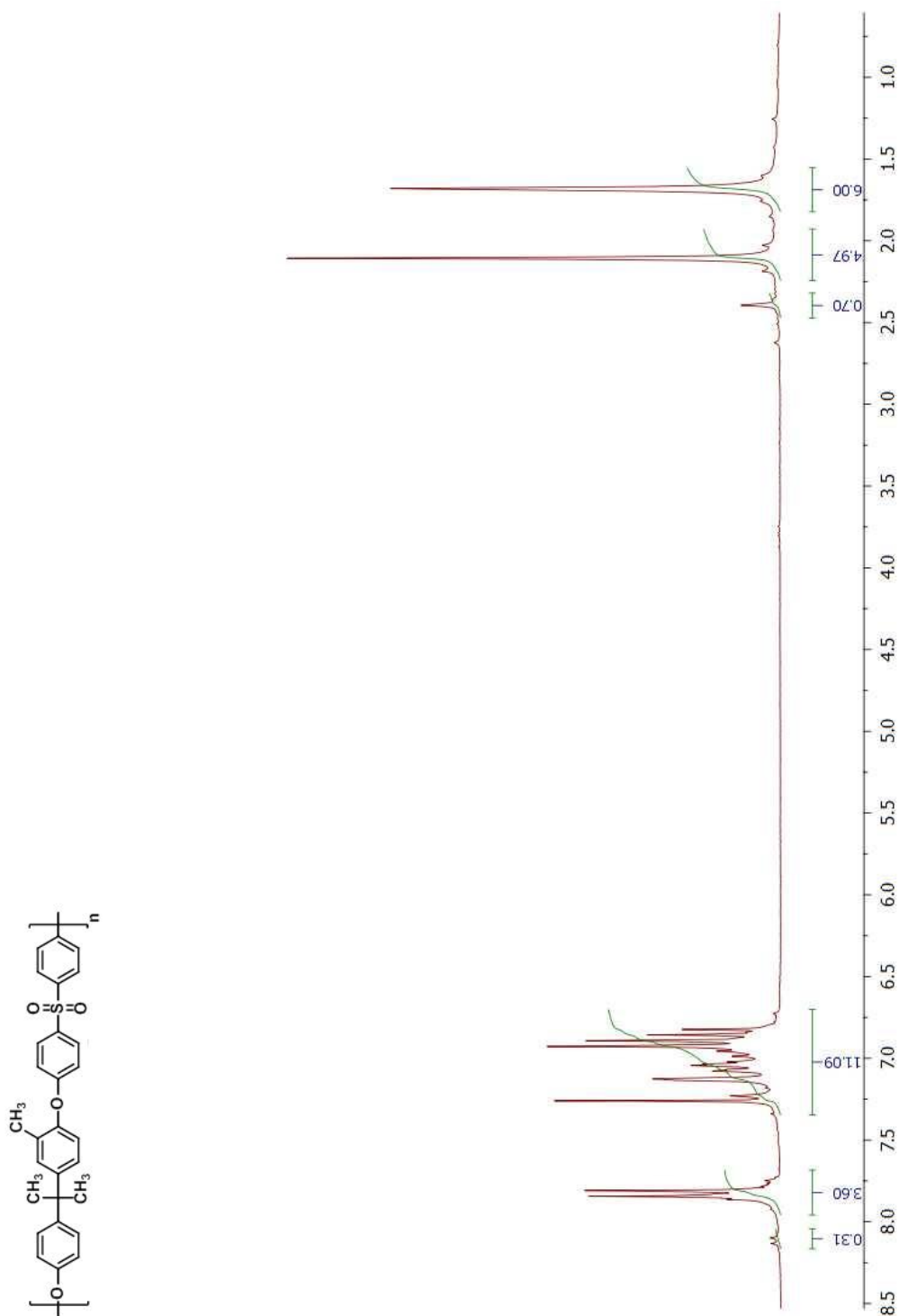
***Ortho*-ether Formylated PSF (3.6) -  $^1\text{H}$  NMR Spectrum (300 MHz,  $\text{CDCl}_3$ )**

**Trichloroacetamidated PSF (3.16) -  $^1\text{H}$  NMR Spectrum (300 MHz,  $\text{CDCl}_3$ )**



Aminomethylated PSF (3.15) -  $^1\text{H}$  NMR Spectrum (300 MHz,  $\text{CDCl}_3$ )

***Ortho*-ether Trimethylsilylated PSF (4.6) -  $^1\text{H}$  NMR Spectrum (300 MHz,  $\text{CDCl}_3$ )**

***Ortho*-ether Methylated PSF (4.25) -  $^1\text{H}$  NMR Spectrum (300 MHz,  $\text{CDCl}_3$ )**

***Ortho*-sulfone Methylated PSF (4.24) -  $^1\text{H}$  NMR Spectrum (300 MHz,  $\text{CDCl}_3$ )**